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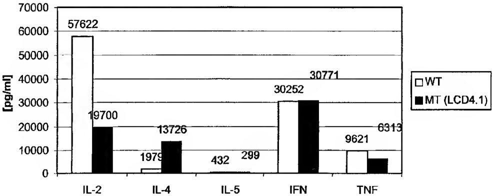
(54) Title: MANIPULATION OF CYTOKINE LEVELS USING CD83 GENE PRODUCTS



(57) Abstract: The invention provides methods for modulating cytokine levels, GM-CSF levels and the immune system using CD83 nucleic acids, CD83 polypeptides, anti-CD83 antibodies and factors that influence CD83 activity or expression. The invention also provides mice having a mutant CD83 gene and mice having a transgenic CD83 gene, which are useful for defining the role of CD83 in the immune system and for identifying compounds that can modulate CD83 and the immune system.

WO 03/045318 A2

MANIPULATION OF CYTOKINE LEVELS USING CD83 GENE PRODUCTS

This application is related to U.S. Application Ser. No. 60/331,958 filed November 21, 2001.

FIELD OF THE INVENTION

The invention relates to an altered CD83 gene product, and methods of modulating cytokine levels by modulating the expression of mutant and wild type CD83 gene products produced in a mammal. The invention also relates to the regulation of T cell and dendritic cell activity and conditions and treatments related thereto.

BACKGROUND OF THE INVENTION

CD83 is a 45 kilodalton glycoprotein that is predominantly expressed on the surface of dendritic cells and other cells of the immune system. Structural analysis of the predicted amino acid sequence of CD83 indicates that it is a member of the immunoglobulin superfamily. *See*, Zhou et al., J. Immunol. 149:735 (1992)). U.S. Patent 5,316,920 and WO 95/29236 disclose further information about CD83. While such information suggests that CD83 plays a role in the immune system, that role is undefined, and the interrelationship of CD83 with cellular factors remains unclear.

Moreover, treatment of many diseases could benefit from more effective methods for increasing or decreasing the immune response. Hence, further information about how to modulate the immune system by using factors such as CD83 are needed.

SUMMARY OF THE INVENTION

The invention provides a method of modulating cytokine levels by modulating the activity or expression of the CD83 gene products. According to the invention, cytokine levels can be modulated in a mammal or in mammalian

cells that are involved in the immune response, for example, antigen presenting cells or T cells.

The invention therefore provides a method of modulating cytokine production in a mammal or in an immune cell by modulating the activity or expression of a CD83 polypeptide. According to the invention, the production of a cytokine such as interleukin-2, interleukin-4, or interlekin-10 can be modulated by modulating the activity or expression of a CD83 polypcptide. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the immune cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention also provides a method of modulating granulocyte macrophage colony stimulating factor production in a mammal or in an immune cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the immune cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention also provides a method of modulating tumor necrosis factor production in a mammal or in a mammalian cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the mammalian cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invcntion further provides a method of inhibiting proliferation of a human peripheral blood mononuclear cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For

example, the antibody can be administered to the mammal or the human peripheral blood mononuclear cell can be contacted with the antibody.

The invention also provides an antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein activated $CD4^+$ T-cells produce lower levels of interleukin-4 when the T-cells are contacted with the antibody. The invention further provides an antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein $CD4^+$ T-cells proliferation is decreased when the T-cells are contacted with the antibody. Such an antibody can have an amino acid sequence that includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64. Nucleic acids encoding such an antibody can have, for example, a sequence that includes SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63 or SEQID NO:65.

The invention also provides a method for decreasing the activity of a CD83 gene product, comprising contacting the CD83 gene product with an antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID

NO:62 or SEQ ID NO:64. The activity of a CD83 gene product can be decreased in a mammal or in a cell that is involved in an immune response, for example, a T cell.

The invention further provides a method for decreasing the translation of a CD83 gene product in a mammalian cell, comprising contacting the mammalian cell with a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

In another embodiment, the invention provides a method for decreasing the translation of a CD83 gene product in a mammal, comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

The invention further provides a method for decreasing proliferation of CD4+ T-cells in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention also provides a method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID

NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention further provides a method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. In some embodiments the interleukin-2 levels are decreased and the interleukin-4 levels are increased to treat an autoimmune disease. In other embodiments, the interleukin-2 levels are decreased and the interleukin-4 levels are increased to stimulate production of Th2-associated cytokines in transplant recipients, for example, to prolong survival of transplanted tissues.

The invention also provides a method for increasing interleukin-10 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention further provides a method for increasing interleukin-10 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. In some embodiments, the interleukin-

10 levels are increased to treat neoplastic disease. In other embodiments, the interleukin-10 levels are increased to treat a tumor.

The invention also provides a method for increasing interleukin-2 levels in a mammal comprising administering to the mammal a functional CD83 polypeptide that comprises SEQ ID NO:9.

The invention further provides a method for increasing interleukin-2 levels in a mammal comprising: (a) transforming a T cell from the mammal with a nucleic acid encoding a functional CD83 polypeptide operably linked to a promoter functional in a mammalian cell, to generate a transformed T cell; (b) administering the transformed T cell to the mammal to provide increased levels of interleukin-2. In some embodiments, the CD83 polypeptide has a sequence that comprises SEQ ID NO:9 or the nucleic acid has a sequence that comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. Such methods for increasing interleukin-2 levels can be used to treat an allergy or an infectious disease.

The invention also provides a method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

Such an antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention further provides a method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic

acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

The invention also provides a method for increasing tumor necrosis factor levels at a selected site in a mammal comprising administering to the site a functional CD83 polypeptide. In another embodiment, the invention provides a method for increasing tumor necrosis factor levels in a selected mammalian cell comprising transforming the cell with a nucleic acid encoding a functional CD83 polypeptide. The CD83 polypeptide employed can, for example, have a sequence comprising SEQ ID NO:9.

Mammals and birds may be treated by the methods and compositions described and claimed herein. Such mammals and birds include humans, dogs, cats, and livestock, for example, horses, cattle, sheep, goats, chickens, turkeys and the like.

The invention further provides a mutant mouse that can serve as an animal model of diminished T cell activation or altered cytokine levels. The mutant mouse has an altered CD83 gene that produces a larger gene product, having SEQ ID NO:4 or containing SEQ ID NO:8. Also provided are methods of using the mutant mouse model to study the effects of cytokines on the immune system, inflammation, the function and regulation of CD83, T cell and dendritic cell activity, the immune response and conditions and treatments related thereto. Hence, the invention further provides a mutant mouse whose somatic and germ cells comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8, wherein expression of the mutant CD83 gene reduces CD4+T cell activation. The mutant CD83 gene can, for example, comprise SEQ ID NO:3.

The invention further provides a method of identifying a compound that can modulate CD4+T cell activation comprising administering a test compound to a mouse having a mutant or wild type transgenic CD83 gene and observing whether CD4+ T cell activation is decreased or increased. The somatic and/or germ cells of the mutant mouse can comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8. Alternatively, the somatic and/or germ cells of the mouse can contain a wild type CD83 gene, for example, SEQ ID NO:1 or SEQ ID NO:9.

The invention also provides a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8. The invention further provides a mutant CD83 gene comprising nucleotide sequence SEQ ID NO:3.

DESCRIPTION OF THE FIGURES

Figure 1 provides flow cytometry data for G3 animals. As shown, reduced numbers of CD4+ T cells are seen in two animals from Pedigree 9, mouse 9.4.1 and mouse 9.4.9. All other animals analyzed on that day exhibit normal numbers of CD4+ T cells.

Figure 2 provides a graph of flow cytometry data for G3 animals. Each diamond symbol represents an individual animal. As shown, multiple animals from the N2 generation exhibit a reduced percentage of CD4+ T cells.

Figure 3 provides the nucleotide sequence of wild type mouse CD83 (SEQ ID NO:1). The ATG start codon and the TGA stop codon are underlined.

Figure 4A-B provides the nucleotide sequence of the mutant CD83 gene (SEQ ID NO:3) of the invention derived from the mutant LCD4.1 animal. The ATG start codon, the mutation and the TGA stop codon are underlined.

Figure 5 provides the amino acid sequence for wild type (top, SEQ ID NO:2) and mutant (bottom, SEQ ID NO:4) CD83 coding regions. The additional C-terminal sequences arising because of the CD83 mutation are underlined.

Figure 6A illustrates that dendritic cells from wild type (♦, WT DC) and mutant (■, mutant DC) mice are capable of the allogeneic activation of CD4+ T cells. CD4+ T cells were stimulated with 10,000, 1000 or 100 dendritic cells for 5 days and proliferation measured by incorporation of tritiated thymidine.

Figure 6B illustrates that CD4+ T cells from mutant mice (■, mutant CD4) fail to respond to allogeneic stimulation with BALBc dendritic cells, although wild type animals (♦, WT CD4+) respond normally. CD4+ T cells were stimulated with 10,000, 1000 or 100 dendritic cells for 5 days and proliferation measured by incorporation of tritiated thymidine.

Figure 7 provides a bar graph illustrating IL-2, IL-4, IL-5, TNFα, and IFNγ production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with 1 μg/ml of anti-CD3 antibodies

and 0.2 μg/ml of anti-CD28 antibodies for 72 hours. As illustrated, IL-2 levels are lower, and IL-4 levels are higher in the CD83 mutant T cells.

Figure 8 provides a bar graph illustrating IL-10 production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with 0.1 μg/ml of anti-CD28 antibodies and 1 to 10 μg/ml of anti-CD3 antibodies for 72 hours. As illustrated, IL-10 levels are higher in the CD83 mutant T cells.

Figure 9 provides a bar graph illustrating GM-CSF production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, GM-CSF production is higher in the CD83 mutant cells than in wild type cells.

Figure 10A provides a bar graph illustrating IL-4 mRNA levels from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, the IL-4 mRNA levels are higher in the CD83 mutant cells.

Figure 10B provides a bar graph illustrating IL-10 mRNA levels from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, the IL-10 mRNA levels are higher in the CD83 mutant cells.

Figure 11 provides a graph illustrating that various preparations of anti-CD83 antibodies inhibit IL-4 production in anti-CD3 and anti-CD28 antibody stimulated T cells. The amount of IL-4 produced by T cells in pg/ml is plotted versus the concentration of different anti-CD83 antibody preparations, including the 20B08 (♦) anti-CD83 preparation, the 20D04 (■) anti-CD83 preparation, the 14C12 (▲) anti-CD83 preparation and the 11G05 (X) anti-CD83 antibody preparation.

Figure 12 provides a graph illustrating that various preparations of anti-CD83 antibodies inhibit T cell proliferation. The graph plots the incorporation of radioactive thymidine in cpms, which was used as an indicator of the amount of T cell proliferation, versus the concentration of the different anti-CD83 antibody preparations, including the 20D04 (♦) anti-CD83 preparation, the 11G05 (■) anti-CD83 antibody preparation, the 14C12 (▲) anti-CD83 preparation and the 6G05 anti-CD83 preparation (X).

Figure 13 provides a graph illustrating that transgenic mice that over-express wild type CD83 have increased T cell proliferation. The graph plots the incorporation of radioactive thymidine in cpms, which was used as an indicator of the amount of T cell proliferation, versus the concentration of OVA peptide. The transgenic mice utilized had a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide that can activate T-cells. When mixed with either transgenic or wild type dendritic cells in the presence of OVA peptide, transgenic CD4+ T cells had increased T-cell proliferation. However, transgenic dendritic cells could not substantially increase wild type CD4+ T cell proliferation. Transgenic CD83 CD4+ T cells mixed with wild type dendritic cells (♦); transgenic CD83 CD4+ T cells mixed with transgenic dendritic cells (■); wild type CD4+ T cells mixed with transgenic dendritic cells (▲); and wild type CD4+ T cells mixed with wild type dendritic cells (X).

Figure 14 provides a schematic diagram of the structural elements included in the mouse CD83 protein used for generating antibodies.

Figure 15 provides a graph of ELISA data illustrating the titer obtained for different isolates of polyclonal anti-CD83 anti-sera. The first (♦), second (■) and third (▲) isolates had similar titers, though the titer of the second isolate (■) was somewhat higher.

Figure 16 illustrates that proliferation of PHA-activated human PBMCs was inhibited by antibodies raised against the external region of the mouse CD83 protein (♦). Pre-immune serum (■) had little effect on the proliferation of human PBMCs.

Figure 17A provides a sequence alignment of anti-CD83 heavy chain variable regions isolated by the invention. Sequences for isolates 20B08H (SEQ ID NO:52), 6G05H (SEQ ID NO:53), 20D04H (SEQ ID NO:54), 11G05 (SEQ ID NO:66) and 14C12 (SEQ ID NO:67) are provided. The CDR regions are highlighted in bold.

Figure 17B provides a sequence alignment of anti-CD83 light chain variable regions isolated by the invention. Sequences for isolates 20B08H (SEQ ID NO:55), 6G05H (SEQ ID NO:56), 20D04H (SEQ ID NO:57), 11G05 (SEQ ID NO:68) and 14C12 (SEQ ID NO:69) are provided. The CDR regions are highlighted in bold.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods for modulating the immune system by using CD83 proteins, CD83 nucleic acids and factors that modulate CD83 activity or expression.

According to the invention, loss or reduction of CD83 activity *in vivo* results in altered cytokine levels, for example, lower interleukin-2 levels, increased interleukin-4 levels, increased GM-CSF levels and increased interleukin-10 levels. Loss or reduction of CD83 activity *in vivo* can also result in decreased numbers of T cells.

Moreover, the invention also relates to increased CD83 activity *in vivo* that can result in altered cytokine levels, for example, higher interleukin-2 levels, decreased interleukin-4 levels, decreased GM-CSF levels and decreased interleukin-10 levels. Increased CD83 expression or activity *in vitro* and *in vivo* can also result in increased activation and increased numbers of T cells.

The effects of CD83 on the immune system, on GM-CSF and on cytokine levels were analyzed by using mutant and transgenic mice. The mutant mouse has an altered CD83 gene that expresses altered (defective) CD83 gene product. The transgenic mouse overexpresses CD83 gene products. Accordingly, the invention provides mammals such as mice that have a mutant or wild type CD83 gene. These mice are useful for identifying the role that CD83 plays in the immune response. These mutant and transgenic animals are useful for identifying factors for manipulating cytokine levels and T cell activation by testing whether those factors and compositions can modulate, inhibit or replace the activity of CD83 *in vivo*.

CD83

CD83 is a lymphocyte and dendritic cell activation antigen that is expressed by activated lymphocytes and dendritic cells. CD83 is also a single-chain cell-surface glycoprotein with a molecular weight of about 45,000 that is believed to be a member of the Ig superfamily. The structure predicted from the CD83 amino acid sequence indicates that CD83 is a membrane glycoprotein with a single extracellular Ig-like domain, a transmembrane domain and cytoplasmic

domain of approximately forty amino acids. The mature CD83 protein has about 186 amino acids and is composed of a single extracellular V type immunoglobulin (Ig)-like domain, a transmembrane domain and a thirty nine amino acid cytoplasmic domain. Northern blot analysis has revealed that CD83 is translated from three mRNA transcripts of about 1.7, 2.0 and 2.5 kb that are expressed by lymphoblastoid cell lines. It is likely that CD83 undergoes extensive post-translational processing because CD83 is expressed as a single chain molecule, but the determined molecular weight is twice the predicted size of the core protein. *See* U.S. Patent 5,766,570.

An example of a human CD83 gene product that can be used in the invention is provided below (SEQ ID NO:9):

```
  1 MSRGLQLLLL SCAYSLAPAT PEVKVACSED VDLPCTAPWD
 41 PQVPYTVSWV KLLEGGEERM ETPQEDHLRG QHYHQKGQNG
 81 SFDAPNERPY SLKIRNTTSC NSGTYRCTLQ DPDGQRNLSG
121 KVILRVTGCP AQRKEETFKK YRAEIVLLLA LVIFYLTLII
161 FTCKFARLQS IFPDFSKAGM ERAFLPVTSP NKHLGLVTPH
201 KTELV
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Such a CD83 gene product can be encoded by a number of different nucleic acids. One example of a human CD83 nucleic acid is provided below (SEQ ID NO:10).

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  1 CCTGGCGCAG CCGCAGCAGC GACGCGAGCG AACTCGGCCG
 41 GGCCCGGGCG CGCGGGGGCG GGACGCGCAC GCGGCGAGGG
 81 CGGCGGGTGA GCCGGGGGCG GGGACGGGGG CGGGACGGGG
121 GCGAAGGGGG CGGGGACGGG GGCGCCCGCC GGCCTAACGG
161 GATTAGGAGG GCGCGCCACC CGCTTCCGCT GCCCGCCGGG
201 GAATCCCCCG GGTGGCGCCC AGGGAAGTTC CCGAACGGGC
241 GGGCATAAAA GGGCAGCCGC GCCGGCGCCC CACAGCTCTG
281 CAGCTCGTGG CAGCGGCGCA GCGCTCCAGC CATGTCGCGC
321 GGCCTCCAGC TTCTGCTCCT GAGCTGCGCC TACAGCCTGG
361 CTCCCGCGAC GCCGGAGGTG AAGGTGGCTT GCTCCGAAGA
401 TGTGGACTTG CCCTGCACCG CCCCCTGGGA TCCGCAGGTT
441 CCCTACACGG TCTCCTGGGT CAAGTTATTG GAGGGTGGTG
481 AAGAGAGGAT GGAGACACCC CAGGAAGACC ACCTCAGGGG
521 ACAGCACTAT CATCAGAAGG GGCAAAATGG TTCTTTCGAC
```

561 GCCCCCAATG AAAGGCCCTA TTCCCTGAAG ATCCGAAACA
601 CTACCAGCTG CAACTCGGGG ACATACAGGT GCACTCTGCA
641 GGACCCGGAT GGGCAGAGAA ACCTAAGTGG CAAGGTGATC
681 TTGAGAGTGA CAGGATGCCC TGCACAGCGT AAAGAAGAGA
721 CTTTTAAGAA ATACAGAGCG GAGATTGTCC TGCTGCTGGC
761 TCTGGTTATT TTCTACTTAA CACTCATCAT TTTCACTTGT
801 AAGTTTGCAC GGCTACAGAG TATCTTCCCA GATTTTTCTA
841 AAGCTGGCAT GGAACGAGCT TTTCTCCCAG TTACCTCCCC
881 AAATAAGCAT TTAGGGCTAG TGACTCCTCA CAAGACAGAA
921 CTGGTATGAG CAGGATTTCT GCAGGTTCTT CTTCCTGAAG
961 CTGAGGCTCA GGGGTGTGCC TGTCTGTTAC ACTGGAGGAG
1001 AGAAGAATGA GCCTACGCTG AAGATGGCAT CCTGTGAAGT
1041 CCTTCACCTC ACTGAAAACA TCTGGAAGGG GATCCCACCC
1081 CATTTTCTGT GGGCAGGCCT CGAAAACCAT CACATGACCA
1121 CATAGCATGA GGCCACTGCT GCTTCTCCAT GGCCACCTTT
1161 TCAGCGATGT ATGCAGCTAT CTGGTCAACC TCCTGGACAT
1201 TTTTTCAGTC ATATAAAAGC TATGGTGAGA TGCAGCTGGA
1241 AAAGGGTCTT GGGAAATATG AATGCCCCCA GCTGGCCCGT
1281 GACAGACTCC TGAGGACAGC TGTCCTCTTC TGCATCTTGG
1321 GGACATCTCT TTGAATTTTC TGTGTTTTGC TGTACCAGCC
1361 CAGATGTTTT ACGTCTGGGA GAAATTGACA GATCAAGCTG
1401 TGAGACAGTG GGAAATATTT AGCAAATAAT TTCCTGGTGT
1441 GAAGGTCCTG CTATTACTAA GGAGTAATCT GTGTACAAAG
1481 AAATAACAAG TCGATGAACT ATTCCCCAGC AGGGTCTTTT
1521 CATCTGGGAA AGACATCCAT AAAGAAGCAA TAAAGAAGAG
1561 TGCCACATTT ATTTTTATAT CTATATGTAC TTGTCAAAGA
1601 AGGTTTGTGT TTTTCTGCTT TTGAAATCTG TATCTGTAGT
1641 GAGATAGCAT TGTGAACTGA CAGGCAGCCT GGACATAGAG
1681 AGGGAGAAGA AGTCAGAGAG GGTGACAAGA TAGAGAGCTA
1721 TTTAATGGCC GGCTGGAAAT GCTGGGCTGA CGGTGCAGTC
1761 TGGGTGCTCG CCCACTTGTC CCACTATCTG GGTGCATGAT
1801 CTTGAGCAAG TTCCTTCTGG TGTCTGCTTT CTCCATTGTA
1841 AACCACAAGG CTGTTGCATG GGCTAATGAA GATCATATAC
1881 GTGAAAATTA TTTGAAAACA TATAAAGCAC TATACAGATT
1921 CGAAACTCCA TTGAGTCATT ATCCTTGCTA TGATGATGGT
1961 GTTTTGGGGA TGAGAGGGTG CTATCCATTT CTCATGTTTT

2001 CCATTGTTTG AAACAAAGAA GGTTACCAAG AAGCCTTTCC
2041 TGTAGCCTTC TGTAGGAATT CTTTTGGGGA AGTGAGGAAG
2081 CCAGGTCCAC GGTCTGTTCT TGAAGCAGTA GCCTAACACA
2121 CTCCAAGATA TGGACACACG GGAGCCGCTG GCAGAAGGGA
2161 CTTCACGAAG TGTTGCATGG ATGTTTTAGC CATTGTTGGC
2201 TTTCCCTTAT CAAACTTGGG CCCTTCCCTT CTTGGTTTCC
2241 AAAGGCATTT ATTGCTGAGT TATATGTTCA CTGTCCCCCT
2281 AATATTAGGG AGTAAAACGG ATACCAAGTT GATTTAGTGT
2321 TTTTACCTCT GTCTTGGCTT TCATGTTATT AAACGTATGC
2361 ATGTGAAGAA GGGTGTTTTT CTGTTTTATA TTCAACTCAT
2401 AAGACTTTGG GATAGGAAAA ATGAGTAATG GTTACTAGGC
2441 TTAATACCTG GGTGATTACA TAATCTGTAC AACGAACCCC
2481 CATGATGTAA GTTTACCTAT GTAACAAACC TGCACTTATA
2521 CCCATGAACT TAAAATGAAA GTTAAAAATA AAAAACATAT
2561 ACAAATAAAA AAAA

A sequence of a wild type mouse CD83 gene that can be used in the invention is provided herein as SEQ ID NO:1. SEQ ID NO:1 is provided below with the ATG start codon and the TGA stop codon identified by underlining.

1 GCGCTCCAGC CGC<u>**ATG**</u>TCGC AAGGCCTCCA GCTCCTGTTT
41 CTAGGCTGCG CCTGCAGCCT GGCACCCGCG ATGGCGATGC
81 GGGAGGTGAC GGTGGCTTGC TCCGAGACCG CCGACTTGCC
121 TTGCACAGCG CCCTGGGACC CGCAGCTCTC CTATGCAGTG
161 TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC
241 CAGGAGAAGG GCCTATTCCC TGACGATCCA AAACACTACC
281 ATCTGCAGCT CGGGCACCTA CAGGTGTGCC CTGCAGGAGC
321 TCGGAGGGCA GCGCAACTTG AGCGGCACCG TGGTTCTGAA
361 GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC
401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG
441 TTGTTTTCTA CCTGACACTC ATCATTTTCA CCTGCAAATT
481 TGCACGACTA CAAAGCATTT TCCCAGATAT TTCTAAACCT
521 GGTACGGAAC AAGCTTTTCT TCCAGTCACC TCCCCAAGCA
561 AACATTTGGG GCCAGTGACC CTTCCTAAGA CAGAAACGGT
601 <u>ATGA</u>GTAGGA TCTCCACTGG TTTTTACAAA GCCAAGGGCA

641 CATCAGATCA GTGTGCCTGA ATGCCACCCG GACAAGAGAA
681 GAATGAGCTC CATCCTCAGA TGGCAACCTT TCTTTGAAGT
721 CCTTCACCTG ACAGTGGGCT CCACACTACT CCCTGACACA
761 GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA
801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG
841 GCTATCTGGT CAACCTCGTG AGTGCTTTTC AGTCATCTAC
881 AAGCTATGGT GAGATGCAGG TGAAGCAGGG TCATGGGAAA
921 TTTGAACACT CTGAGCTGGC CCTGTGACAG ACTCCTGAGG
961 ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA
1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC
1041 TGGCGGAAAT TGACAGGCCA AGCTGTGAGC CAGTGGGAAA
1081 TATTTAGCAA ATAATTTCCC AGTGCGAAGG TCCTGCTATT
1121 AGTAAGGAGT ATTATGTGTA CATAGAAATG AGAGGTCAGT
1161 GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA
1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT
1241 TTTTAATCTT CATGTACTTG TCAAAGAAGA ATTTTTCATG
1281 TTTTTTCAAA GAAGTGTGTT TCTTTCCTTT TTTAAAATAT
1321 GAAGGTCTAG TTACATAGCA TTGCTAGCTG ACAAGCAGCC
1361 TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA
1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA
1441 CAATGGACTG AGAAACCAGA AGTCTGGCCA CAAGATTGTC
1481 TGTATGATTC TGGACGAGTC ACTTGTGGTT TTCACTCTCT
1521 GGTTAGTAAA CCAGATAGTT TAGTCTGGGT TGAATACAAT
1561 GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT
1641 AGAGTTCTGG AGCTGAGCGA ATGCCTGTCA TATCTCAGCT
1681 TGCCCATCAA TCCAAACACA GGAGGCTACA AAAAGGACAT
1721 GAGCATGGTC TTCTGTGTGA ACTCCTCCTG AGAAACGTGG
1761 AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG
1841 ACAGGAGGAA GTTCTCAGAT GTTGCATTGA TGTAACATTG
1881 TTGCATTTCT TTAATGAGCT GGGCTCCTTC CTCATTTGCT
1921 TCCCAAAGAG ATTTTGTCCC ACTAATGGTG TGCCCATCAC
1961 CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA
2041 ATGCATGTGA A

Nucleic acids having SEQ ID NO:1 encode a mouse polypeptide having SEQ ID NO:2, provided below.

```
  1 MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP
 41 WDPQLSYAVS WAKVSESGTE SVELPESKQN SSFEAPRRRA
 81 YSLTIQNTTI CSSGTYRCAL QELGGQRNLS GTVVLKVTGC
121 PKEATESTFR KYRAEAVLLF SLVVFYLTLI IFTCKFARLQ
161 SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETV
```

According to the invention, loss or reduction of CD83 activity *in vivo* results in altered cytokine levels, for example, lower interleukin-2 levels, increased interleukin-4 levels, increased GM-CSF levels and increased interleukin-10 levels. Loss or reduction of CD83 activity *in vivo* can also result in decreased numbers of T cells.

Moreover, increased CD83 activity *in vivo* can also result in altered cytokine levels, for example, higher interleukin-2 levels, decreased interleukin-4 levels, decreased GM-CSF levels and decreased interleukin-10 levels. Increased CD83 expression or activity *in vivo* can also result in increased activation or increased numbers of T cells.

The effect of CD83 on cytokine levels was ascertained through use of a mutant mouse that encodes a mutant CD83. Such a mutant mouse has a CD83 gene encoding SEQ ID NO:4, with added C-terminal sequences provided by SEQ ID NO:8. In contrast to these wild type CD83 nucleic acids and polypeptides, the mutant CD83 gene of the invention has SEQ ID NO:3. SEQ ID NO:3 is provided below with the ATG start codon, the mutation, and the TGA stop codon are identified by underlining.

```
  1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTTT
 41 CTAGGCTGCG CCTGCAGCCT GGCACCCGCG ATGGCGATGC
 81 GGGAGGTGAC GGTGGCTTGC TCCGAGACCG CCGACTTGCC
121 TTGCACAGCG CCCTGGGACC CGCAGCTCTC CTATGCAGTG
161 TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC
241 CAGGAGAAGG GCCTATTCCC TGACGATCCA AAACACTACC
```

281 ATCTGCAGCT CGGGCACCTA CAGGTGTGCC CTGCAGGAGC
321 TCGGAGGGCA GCGCAACTTG AGCGGCACCG TGGTTCTGAA
361 GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC
401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG
441 TTGTTTTCTA CCTGACACTC ATCATTTTCA CCTGCAAATT
481 TGCACGACTA CAAAGCATTT TCCCAGATAT TTCTAAACCT
521 GGTACGGAAC AAGCTTTTCT TCCAGTCACC TCCCCAAGCA
561 AACATTTGGG GCCAGTGACC CTTCCTAAGA CAGAAACGGT
601 AAGAGTAGGA TCTCCACTGG TTTTTACAAA GCCAAGGGCA
641 CATCAGATCA GTGTGCCTGA ATGCCACCCG GACAAGAGAA
681 GAATGAGCTC CATCCTCAGA TGGCAACCTT TCTTTGAAGT
721 CCTTCACCTG ACAGTGGGCT CCACACTACT CCCTGACACA
761 GGGTCTT**GA**G CACCATCATA TGATCACGAA GCATGGAGTA
801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG
841 GCTATCTGGT CAACCTCGTG AGTGCTTTTC AGTCATCTAC
881 AAGCTATGGT GAGATGCAGG TGAAGCAGGG TCATGGGAAA
921 TTTGAACACT CTGAGCTGGC CCTGTGACAG ACTCCTGAGG
961 ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA
1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC
1041 TGGCGGAAAT TGACAGGCCA AGCTGTGAGC CAGTGGGAAA
1081 TATTTAGCAA ATAATTTCCC AGTGCGAAGG TCCTGCTATT
1121 AGTAAGGAGT ATTATGTGTA CATAGAAATG AGAGGTCAGT
1161 GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA
1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT
1241 TTTTAATCTT CATGTACTTG TCAAAGAAGA ATTTTTCATG
1281 TTTTTTCAAA GAAGTGTGTT TCTTTCCTTT TTTAAAATAT
1321 GAAGGTCTAG TTACATAGCA TTGCTAGCTG ACAAGCAGCC
1361 TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA
1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA
1441 CAATGGACTG AGAAACCAGA AGTCTGGCCA CAAGATTGTC
1481 TGTATGATTC TGGACGAGTC ACTTGTGGTT TTCACTCTCT
1521 GGTTAGTAAA CCAGATAGTT TAGTCTGGGT TGAATACAAT
1561 GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT
1641 AGAGTTCTGG AGCTGAGCGA ATGCCTGTCA TATCTCAGCT
1681 TGCCCATCAA TCCAAACACA GGAGGCTACA AAAAGGACAT

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1721 GAGCATGGTC TTCTGTGTGA ACTCCTCCTG AGAAACGTGG
1761 AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG
1841 ACAGGAGGAA GTTCTCAGAT GTTGCATTGA TGTAACATTG
1881 TTGCATTTCT TTAATGAGCT GGGCTCCTTC CTCATTTGCT
1921 TCCCAAAGAG ATTTTGTCCC ACTAATGGTG TGCCCATCAC
1961 CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA
2041 ATGCATGTGA A
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The change from a thymidine in SEQ ID NO:1 to an adenine in SEQ ID NO:3 at the indicated position (602) leads to read-through translation because the stop codon at positions 602-604 in SEQ ID NO:1 is changed to a codon that encodes an arginine. Accordingly, mutant CD83 nucleic acids having SEQ ID NO:3 encode an elongated polypeptide having SEQ ID NO:4, provided below, where the extra amino acids are underlined.

```
  1 MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP
 41 WDPQLSYAVS WAKVSESGTE SVELPESKQN SSFEAPRRRA
 81 YSLTIQNTTI CSSGTYRCAL QELGGQRNLS GTVVLKVTGC
121 PKEATESTFR KYRAEAVLLF SLVVFYLTLI IFTCKFARLQ
161 SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETVRVGS
201 PLVFTKPRAH QISVPECHPD KRRMSSILRW QPFFEVLHLT
241 VGSTLLPDTG S
```

In another embodiment, the invention provides mutant CD83 nucleic acids that include SEQ ID NO:5.

```
  1 ATGTCGCAAG GCCTCCAGCT CCTGTTTCTA GGCTGCGCCT
 41 GCAGCCTGGC ACCCGCGATG GCGATGCGGG AGGTGACGGT
 81 GGCTTGCTCC GAGACCGCCG ACTTGCCTTG CACAGCGCCC
121 TGGGACCCGC AGCTCTCCTA TGCAGTGTCC TGGGCCAAGG
161 TCTCCGAGAG TGGCACTGAG AGTGTGGAGC TCCCGGAGAG
201 CAAGCAAAAC AGCTCCTTCG AGGCCCCCAG GAGAAGGGCC
241 TATTCCCTGA CGATCCAAAA CACTACCATC TGCAGCTCGG
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281  GCACCTACAG GTGTGCCCTG CAGGAGCTCG GAGGGCAGCG
321  CAACTTGAGC GGCACCGTGG TTCTGAAGGT GACAGGATGC
361  CCCAAGGAAG CTACAGAGTC AACTTTCAGG AAGTACAGGG
401  CAGAAGCTGT GTTGCTCTTC TCTCTGGTTG TTTTCTACCT
441  GACACTCATC ATTTTCACCT GCAAATTTGC ACGACTACAA
481  AGCATTTTCC CAGATATTTC TAAACCTGGT ACGGAACAAG
521  CTTTTCTTCC AGTCACCTCC CCAAGCAAAC ATTTGGGGCC
561  AGTGACCCTT CCTAAGACAG AAACGGTAAG AGTAGGATCT
601  CCACTGGTTT TTACAAAGCC AAGGGCACAT CAGATCAGTG
641  TGCCTGAATG CCACCCGGAC AAGAGAAGAA TGAGCTCCAT
681  CCTCAGATGG CAACCTTTCT TTGAAGTCCT TCACCTGACA
721  GTGGGCTCCA CACTACTCCC TGACACAGGG TCTTGA
```

Nucleic acids having SEQ ID NO:5 also encode a polypeptide having SEQ ID NO:4.

In another embodiment, the invention provides mutant CD83 nucleic acids that include SEQ ID NO:7.

```
  1  AGAGTAGGAT CTCCACTGGT TTTTACAAAG CCAAGGGCAC
 41  ATCAGATCAG TGTGCCTGAA TGCCACCCGG ACAAGAGAAG
 81  AATGAGCTCC ATCCTCAGAT GGCAACCTTT CTTTGAAGTC
121  CTTCACCTGA CAGTGGGCTC CACACTACTC CCTGACACAG
161  GGTCTTGA
```

The invention also provides a mutant CD83 containing SEQ ID NO:8, provided below.

```
  1  RVGSPLVFTK PRAHQISVPE CHPDKRRMSS ILRWQPFFEV
 41  LHLTVGSTLL PDTGS
```

SEQ ID NO:8 contains read through sequences that are not present in the wild type CD83 polypeptide but are present in the mutant CD83 gene product provided by the invention.

CD83 Modulation of Cytokine Levels

The invention also provides compositions and methods for increasing interleukin-4 levels, increasing GM-CSF levels, increasing interleukin-10 levels and decreasing interleukin-2 levels in a mammal. Such compositions and methods generally operate by decreasing the expression or function of CD83 gene products in the mammal. Interleukin-4 promotes the differentiation of Th2 cells while decreasing the differentiation of precursor cells into Th1 cells. Th2 cells are involved in helping B lymphocytes and in stimulating production of IgG1 and IgE antibodies. Enhancement of Th2 formation may be useful, for example, in autoimmune diseases and in organ transplantation.

Alternatively, the invention provides compositions and methods for decreasing interleukin-4 levels, decreasing interleukin-10 levels and increasing interleukin-2 levels in a mammal. Such compositions and methods generally increase the expression or function of CD83 gene products in the mammal. Interleukin-2 promotes the differentiation of Th1 cells and decreases the differentiation of Th-2 cells. Th1 cells are, for example, involved in inducing autoimmune and delayed type hypersensitivity responses. Inhibition of Th2 formation may be useful in treating allergic diseases, malignancies and infectious diseases.

CD4+T helper cells are not a homogeneous population but can be divided on the basis of cytokine secretion into at least two subsets termed T helper type 1 (Th1) and T helper type 2 (Th2) (see e.g., Mosmann, T. R. et al. (1986) J. Immunol. 136:2348-2357; Paul, W. E. and Seder, R. A. (1994) Cell 76:241-251; Seder, R. A. and Paul, W. E. (1994) Ann. Rev. Immunol. 12:635-673). Th1 cells secrete interleukin-2 (IL-2) and interferon-γ (IFN-γ) while Th2 cells produce interleukin-4 (IL4), interleukin-5 (IL-5), interleukin-10 (IL-10) and interleukin-13 (IL-13). Both subsets produce cytokines such as tumor necrosis factor (TNF) and granulocyte/macrophage-colony stimulating factor (GM-CSF).

In addition to their different pattern of cytokine expression, Th1 and Th2 cells are thought to have differing functional activities. For example, Th1 cells are involved in inducing delayed type hypersensitivity responses, whereas Th2 cells are involved in providing efficient "help" to B lymphocytes and stimulating production of IgG1 and IgE antibodies.

The ratio of Th1 to Th2 cells is highly relevant to the outcome of a wide array of immunologically-mediated clinical diseases including autoimmune, allergic and infectious diseases. For example, in experimental leishmania infections in mice, animals that are resistant to infection mount predominantly a Th1 response, whereas animals that are susceptible to progressive infection mount predominantly a Th2 response (Heinzel, F. P., et al. (1989) J. Exp. Med. 169:59-72; Locksley, R. M. and Scott, P. (1992) Immunoparasitology Today 1:A58-A6 1). In murine schistosomiasis, a Th1 to Th2 switch is observed coincident with the release of eggs into the tissues by female parasites and is associated with a worsening of the disease condition (Pearce, E. J., et al. (1991) J. Exp. Med. 173:159-166; Grzych, J-M.,et al. (1991) J. Immunol 141:1322-1327; Kullberg, M. C., et al. (1992) J. Immunol. 148:3264-3270).

Many human diseases, including chronic infections (such as with human immunodeficiency virus (HIV) and tuberculosis) and certain metastatic carcinomas, also are characterized by a Th1 to Th2 switch (see e.g., Shearer, G. M. and Clerici, M. (1992) Prog. Chem. Immunol. 54:21-43; Clerici, M and Shearer, G. M. (1993) Immunology Today 14:107-111; Yamamura, M., et al. (1993) J Clin. Invest. 91:1005-1010; Pisa, P., et al. (1992) Proc. Natl. Acad. Sci. USA 89:7708-7712; Fauci, A. S. (1988) Science 239:617-623).

Certain autoimmune diseases have been shown to be associated with a predominant Th1 response. For example, patients with rheumatoid arthritis have predominantly Th1 cells in synovial tissue (Simon, A. K., et al. (1994) Proc. Natl. Acad. Sci. USA 91:8562-8566) and experimental autoimmune encephalomyelitis (EAE) can be induced by autoreactive Th1 cells (Kuchroo, V. K., et al. (1993) J. Immunol. 151:4371-4381).

The ability to alter or manipulate ratios of Th1 and Th2 subsets requires an understanding of the mechanisms by which the differentiation of CD4 T helper precursor cells (Thp), which secrete only IL-2, choose to become Th1 or Th2 effector cells. It is clear that the cytokines themselves are potent Th cell inducers and form an autoregulatory loop (see e.g., Paul, W. E. and Seder, R. A. (1994) Cell 76:241-251; Seder, R. A. and Paul, W. E. (1994) Ann. Rev. Immunol. 12:635-673). Thus, IL4 promotes the differentiation of Th2 cells while

preventing the differentiation of precursors into Th1 cells, while IL-12 and IFN-γ have the opposite effect.

According to the invention, one way to alter Th1:Th2 ratios is to increase or decrease the level of selected cytokines by using CD83. Direct administration of cytokines or antibodies to cytokines has been shown to have an effect on certain diseases mediated by either Th1 or Th2 cells. For example, administration of recombinant IL-4 or antibodies to IL-12 ameliorate EAE, a Th1-driven autoimmune disease (see Racke; M. K. et al. (1994) J. Exp. Med. 180:1961-1966; and Leonard, J. P. et al. (1995) J. Exp. Med. 181:381-386), while anti-IL-4 antibodies can ameliorate the Th2-mediated parasitic disease, Leishmania major (Sadick, M. D. et al. (1990) J. Exp. Med. 171:115-127).

Numerous disease conditions are associated with either a predominant Th1-type response or a predominant Th2-type response and the individuals suffering from such disease conditions could benefit from treatment with the CD83 related compositions and methods of the invention. Application of the immunomodulatory methods of the invention to such diseases is described in further detail below.

Allergies

Allergies are mediated through IgE antibodies whose production is regulated by the activity of Th2 cells and the cytokines produced thereby. In allergic reactions, IL-4 is produced by Th2 cells, which further stimulates production of IgE antibodies and activation of cells that mediate allergic reactions, i.e., mast cells and basophils. IL-4 also plays an important role in eosinophil mediated inflammatory reactions.

Accordingly, the stimulation of CD83 production by use of the compositions and methods of the invention can be used to inhibit the production of Th2-associated cytokines, for example IL-4, in allergic patients as a means to down-regulate production of pathogenic IgE antibodies. A stimulatory agent may be directly administered to the subject mammal. Alternatively, the CD83 stimulatory agent (e.g. CD83 expression cassette) can be administered to cells (e.g., Thp cells or Th2 cells) that may be obtained from the subject and those modified cells can be readministered to the subject mammal. Moreover, in

certain situations it may be beneficial to co-administer the allergen together with the stimulatory agent either to the subject or to cells treated with the stimulatory agent. Such co-administration can inhibit (e.g., desensitize) the allergen-specific response. The treatment may be further enhanced by administering Th1-promoting agents, such as the cytokine IL-12 or antibodies to Th2-associated cytokines (e.g., anti-IL-4 antibodies), to the allergic subject in amounts sufficient to further stimulate a Th1-type response.

Cancer

The invention also relates to CD83-related methods for increasing interleukin-10 (IL-10) levels to reduce the spread of neoplastic diseases and/or prevent neoplastic diseases and the growth of a tumor. According to the invention, decreased CD83 activity can dramatically increase the levels of IL-10 in the body and such increased interleukin-10 can be used to treat neoplastic diseases. Hence, the invention provides a method for preventing or treating tumors in a mammal, which involves diminishing CD83 expression or activity in the mammal. In various embodiments, the tumor is IL-2-dependent, a plasmacytoma, or a leukemia, including a lymphocytic leukemia such as a B cell lymphocytic leukemia.

The invention also provides methods for increasing T cell activation or T cell proliferation by increasing CD83 activity or expression. Such methods can also be used to prevent or treat tumors in a mammal.

Infectious Diseases

The expression of Th2-promoting cytokines also has been reported to increase during a variety of infectious diseases. For example, HIV infection, tuberculosis, leishmaniasis, schistosomiasis, filarial nematode infection, intestinal nematode infection and other such infectious diseases are associated with a Th1 to Th2 shift in the immune response. See e.g., Shearer, G. M. and Clerici, M. (1992) Prog. Chem. Immunol. 54:2143; Clerici, M and Shearer, G. M. (1993) Immunology Today 14:107-111; Fauci, A. S. (1988) Science 239:617-623; Locksley, R. M. and Scott, P. (1992) Immunoparasitology Today 1:A58-A61; Pearce, E. J., et al. (1991) J. Exp. Med. 173:159-166; Grzych,J-M., et al.

(1991) J. Immunol. 141:1322-1327; Kullberg, M. C., et al. (1992) J. Immunol. 148:3264-3270; Bancroft, A. J., et al. (1993) J. Immunol 150:1395-1402; Pearlman, E., et al. (11993) Infect. Immun. 61:1105-1112; Else, K. J., et al. (1994) J. Exp. Med. 179:347-351.

Accordingly, the stimulatory CD83-related compositions and methods of the invention can be used to inhibit the production of Th2-cells in subjects with infectious diseases to promote an ongoing Th1 response in the patients and to ameliorate the course of the infection. The treatment may be further enhanced by administering other Th1-promoting agents, such as the cytokine IL-12 or antibodies to Th2-associated cytokines (e.g., anti-IL-4 antibodies), to the recipient in amounts sufficient to further stimulate a Th 1-type response.

Hence, for example, infections of the following microbial organisms can be treated by the methods of the invention: *Aeromonas* spp., *Bacillus* spp., *Bacteroides* spp., *Campylobacter* spp., *Clostridium* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Gastrospirillum* sp., *Helicobacter* spp., *Klebsiella* spp., *Salmonella* spp., *Shigella* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Vibrio* spp., *Yersinia* spp., and the like. Infections that can be treated by the methods of the invention include those associated with staph infections (*Staphylococcus aureus*), typhus (*Salmonella typhi*), food poisoning (*Escherichia coli*, such as O157:H7), bascillary dysentery (*Shigella dysenteria*), pneumonia (*Psuedomonas aerugenosa* and/or *Pseudomonas cepacia*), cholera (*Vivrio cholerae*), ulcers (*Helicobacter pylori*) and others. *E. coli* serotype 0157:H7 has been implicated in the pathogenesis of diarrhea, hemorrhagic colitis, hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). The methods of the invention are also active against drug-resistant and multiply-drug resistant strains of bacteria, for example, multiply-resistant strains of *Staphylococcus aureus* and vancomycin-resistant strains of *Enterococcus faecium* and *Enterococcus faecalis*.

The methods of the invention are also effective against viruses. The term "virus" refers to DNA and RNA viruses, viroids, and prions. Viruses include both enveloped and non-enveloped viruses, for example, hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), poxviruses, herpes viruses, adenoviruses, papovaviruses, parvoviruses,

reoviruses, orbiviruses, picornaviruses, rotaviruses, alphaviruses, rubivirues, influenza virus type A and B, flaviviruses, coronaviruses, paramyxoviruses, morbilliviruses, pneumoviruses, rhabdoviruses, lyssaviruses, orthmyxoviruses, bunyaviruses, phleboviruses, nairoviruses, hepadnaviruses, arenaviruses, retroviruses, enteroviruses, rhinoviruses and the filovirus.

Autoimmune Diseases

The CD83-related compositions and methods of the invention can be used in the treatment of autoimmune diseases that are associated with a Th2-type dysfunction. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against "self tissues" and that promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Modulation of T helper-type responses can have an effect on the course of the autoimmune disease. For example, in experimental allergic encephalomyelitis, stimulation of a Th2-type response by administration of IL-4 at the time of the induction of the disease diminishes the intensity of the autoimmune disease (Paul, W. E., et al. (1994) Cell 76:241-251). Furthermore, recovery of the animals from the disease has been shown to be associated with an increase in a Th2-type response as evidenced by an increase of Th2-specific cytokines (Koury, S. J., et al. (1992) J Exp. Med. 176:1355-1364). Moreover, T cells that can suppress EAE secrete Th2-specific cytokines (Chen, C., et al. (1994) Immunity 1:147-154). Since stimulation of a Th2-type response in experimental allergic encephalomyelitis has a protective effect against the disease, stimulation of a Th2 response in subjects with multiple sclerosis (for which EAE is a model) is likely to be beneficial therapeutically.

Similarly, stimulation of a Th2-type response in type I diabetes in mice provides a protective effect against the disease. Indeed, treatment of NOD mice with IL-4 (which promotes a Th2 response) prevents or delays onset of type I diabetes that normally develops in these mice (Rapoport, M. J., et al. (1993) J. Exp. Med. 178:87-99). Thus, inhibition of CD83 production can stimulate IL-4 production and/or a Th2 response in a subject suffering from or susceptible to diabetes may ameliorate the effects of the disease or inhibit the onset of the disease.

Yet another autoimmune disease in which stimulation of a Th2-type response may be beneficial is rheumatoid arthritis (RA). Studies have shown that patients with rheumatoid arthritis have predominantly Th1 cells in synovial tissue (Simon, A. K., et al., (1994) Proc. Natl. Acad. Sci. USA 91:8562-8566). By stimulating a Th2 response in a subject with rheumatoid arthritis, the detrimental Th1 response can be concomitantly down-modulated to thereby ameliorate the effects of the disease.

Accordingly, the CD83-related compositions and methods of the invention can be used to stimulate production of Th2-associated cytokines in subjects suffering from, or susceptible to, an autoimmune disease in which a Th2-type response is beneficial to the course of the disease. Such compositions and methods would modulate CD83 activity. In some embodiments, the compositions would decrease CD83 activity and thereby increase the level of certain cytokines, for example, IL-4 levels are increased when CD83 activity is diminished. The treatment may be further enhanced by administering other Th2-promoting agents, such as IL-4 itself or antibodies to Th1-associated cytokines, to the subject in amounts sufficient to further stimulate a Th2-type response. The treatment may be further enhanced by administering a Th1-promoting cytokine (e.g., IFN-γ) to the subject in amounts sufficient to further stimulate a Th1-type response.

The efficacy of CD83-related for treating autoimmune diseases can be tested in the animal models provided herein or other models of human diseases (e.g., EAE as a model of multiple sclerosis and the NOD mice as a model for diabetes). Such animal models include the mrl/lpr/lpr mouse as a model for lupus erythematosus, murine collagen-induced arthritis as a model for rheumatoid arthritis, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856). A CD83-modulatory (i.e., stimulatory or inhibitory) agent of the invention is administered to test animals and the course of the disease in the test animals is then monitored by the standard methods for the particular model being used. Effectiveness of the modulatory agent is evidenced by amelioration of the disease condition in animals treated with the agent as compared to untreated animals (or animals treated with a control agent).

Non-limiting examples of autoimmune diseases and disorders having an autoimmune component that may be treated according to the invention include diabetes mellitus, arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis), multiple sclerosis, myasthenia gravis, systemic lupus erythematosis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjogren's Syndrome, including keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, uveitis posterior, and interstitial lung fibrosis.

Transplantation

While graft rejection or graft acceptance may not be attributable exclusively to the action of a particular T cell subset (i.e., Th1 or Th2 cells) in the graft recipient, studies have implicated a predominant Th2 response in prolonged graft survival and a predominant Th1 response in graft rejection (for a discussion see Dallman, M. J. (1995) Curr. Opin. Immunol. 7:632-638; Takeuchi, T. et al. (1992) Transplantation 53:1281-1291; Tzakis, A. G. et al. (1994) J. Pediatr. Surg. 29:754-756; Thai, N. L. et al. (1995) Transplantation 59:274-281. Additionally, adoptive transfer of cells having a Th2 cytokine phenotype prolongs skin graft survival (Maeda, H. et al. (1994) Int. Immunol. 6:855-862) and reduces graft-versus-host disease (Fowler, D. H. et al. (1994) Blood 84:3540-3549; Fowler, D. H. et al. (1994) Prog. Clin. Biol. Res. 389:533-540). Furthermore, administration of IL-4, which promotes Th2 differentiation, prolongs cardiac allograft survival (Levy, A. E. and Alexander, J. W. (1995)

Transplantation 60:405-406), whereas administration of IL-12 in combination with anti-IL-10 antibodies, which promotes Th1 differentiation, enhances skin allograft rejection (Gorczynski, R. M. et al. (1995) Transplantation 60:1337-1341).

As provided herein, loss of CD83 function increases interleukin-4 production, which in turn promotes the differentiation of Th2 cells and depresses the differentiation of precursor cells into Th1 cells. Accordingly, methods of the invention that involve decreasing CD83 function can be used to stimulate production of Th2-associated cytokines in transplant recipients to prolong survival of the graft. These methods can be used both in solid organ transplantation and in bone marrow transplantation (e.g., to inhibit graft-versus-host disease). These methods can involve either direct administration of a CD83 inhibitory agent to the transplant recipient or ex vivo treatment of cells obtained from the subject (e.g., Thp, Th1 cells, B cells, non-lymphoid cells) with an inhibitory agent followed by readministration of the cells to the subject. The treatment may be further enhanced by administering other Th2-promoting agents, such as IL-4 itself or antibodies to Th1-associated cytokines, to the recipient in amounts sufficient to further stimulate a Th2-type response.

Additional Methods of Using CD83

In addition to the foregoing disease situations, the modulatory methods of the invention also are useful for other purposes.

For example, inhibition of CD83 activity or function gives rise to increased granulocyte macrophage-colony stimulating factor (GM-CSF). Granulocyte macrophage colony stimulating factor is a hematopoietic growth factor that promotes the proliferation and differentiation of hematopoietic progenitor cells. GM-CSF is approved for treatment of patients requiring increased proliferation of white blood cells. Data indicates that GM-CSP is also useful as a vaccine adjuvant Morrissey, et al., J. Immunology 139, 1113-1119 (1987). GM-CSF can also be used to treat patients prone to infection such as those undergoing high risk bowel surgery, trauma victims and individuals with HIV.

Accordingly, the invention provides a method of increasing the levels of

GM-CSF in a mammal or in a mammalian cell by administering an agent that modulates or inhibits CD83 activity or expression.

The invention also provides a method of decreasing the levels of GM-CSF in a mammal or in a mammalian cell by administering an agent that modulates or stimulates CD83 activity or expression.

Moreover, in other embodiments the CD83 inhibitory methods of the invention can be used to stimulate production of IL-4 or IL-10 in vitro for commercial production of these cytokines. For example, CD4+ T cells with a null or other mutation in the CD83 gene can be cultured and then stimulated to produce cytokines, for example, by use of anti-CD3 and/or anti-CD28 antibodies to activate the mutant CD4+ T cells. Significant amounts of IL-4 and IL-10 can then be isolated from the culture media. Alternatively, CD4+ T cells can be contacted with the CD83 inhibitory agent in vitro to stimulate IL-4 or IL-10 production and the IL-4 or IL-10 can be recovered from the culture supernatant. The isolated IL-4 and/or IL-10 can be further purified if necessary, and packaged for commercial use.

The methods of the invention can be adapted to vaccinations to promote either a Th1 or a Th2 response to an antigen of interest in a subject. That is, CD83 or CD83 modulators of the invention can serve as adjuvants to direct an immune response to a vaccine either to a Th1 response or a Th2 response. For example, to stimulate an antibody response to an antigen of interest (i.e., for vaccination purposes), the antigen and a CD83 inhibitory agent of the invention can be coadministered to a subject to promote a Th2 response to the antigen in the subject, since Th2 responses provide efficient B cell help and promote IgG1 production.

Alternatively, to promote a cellular immune response to an antigen of interest, the antigen and a CD83 stimulating agent of the invention can be coadministered to a subject to promote a Th1 response to the antigen in a subject, since Th1 responses favor the development of cell-mediated immune responses (e.g., delayed hypersensitivity responses).

The antigen of interest and the modulatory agent can be formulated together into a single pharmaceutical composition or in separate compositions.

Thus, in some embodiments, the antigen of interest and the modulatory agent are administered simultaneously to the subject. Alternatively, in certain situations it may be desirable to administer the antigen first and then the modulatory agent or vice versa. For example, in the case of an antigen that naturally evokes a Th1 response, it may be beneficial to first administer the antigen alone to stimulate a Th1 response and then administer a CD83 inhibitory agent, alone or together with a boost of antigen, to shift the immune response to a Th2 response.

According to the invention, any agent that can modulate CD83 to increase or decrease cytokine levels, increase or decrease T cell levels or produce any other CD83-related response can be used in the compositions and methods of the invention. In some embodiments, anti-CD83 antibodies of the invention are used to either activate or inhibit CD83 activity. Activation or inhibition by such antibodies can depend on the epitope to which the antibody binds. Hence, antibodies may play a role in boosting or depressing CD83 activity. These CD83 modulatory agents, including anti-CD83 antibodies, are described in more detail below.

Stimulating or Inhibiting CD83

According to the invention, any agent that can stimulate CD83 to perform its natural functions can be used in the compositions and methods of the invention as a CD83 stimulatory agent. Indicators that CD83 activity is stimulated include increased IL-2 cytokine levels, increased T cell levels, and increased TNF levels relative to unstimulated levels in wild type CD83 cells. Examples of CD83 stimulatory agents include, for example, the CD83 gene product itself, certain anti-CD83 antibodies, CD83-encoding nucleic acids (DNA or RNA), factors that promote CD83 transcription or translation, organic molecules, peptides and the like.

Also, according to the invention, any agent that can inhibit CD83 from performing its natural functions can be used in the compositions and methods of the invention as a CD83 inhibitory agent. Indicators that CD83 activity is inhibited include increased IL-4 cytokine levels, increased IL-10 levels, decreased IL-2

production, decreased T cell levels, and decreased TNF levels relative to uninhibited levels in wild type CD83 cells.

Examples of CD83 inhibitors include anti-CD83 antibodies, CD83 anti-sense nucleic acids (e.g. nucleic acids that can hybridize to CD83 nucleic acids), organic compounds, peptides and agents that can mutate an endogenous CD83 gene. In some embodiments, the CD83 stimulatory or inhibitory agents are proteins, for example, CD83 gene products, anti-CD83 antibody preparations, CD83 inhibitors, peptides and protein factors that can promote CD83 transcription or translation. In other embodiments, the CD83 stimulatory or inhibitory agents are peptides or organic molecules. Such proteins, organic molecules and organic molecules can be prepared and/or purified as described herein or by methods available in the art, and administered as provided herein.

In other embodiments, the CD83 stimulatory or inhibitory agents can be nucleic acids including recombinant expression vectors or expression cassettes encoding CD83 gene products, CD83 transcription factors, CD83 anti-sense nucleic acid, intracellular antibodies capable of binding to CD83 or dominant negative CD83 inhibitors. Such nucleic acids can be operably linked to a promoter that is functional in a mammalian cell, and then introduced into cells of the subject mammal using methods known in the art for introducing nucleic acid (e.g., DNA) into cells.

The "promoter functional in a mammalian cell" or "mammalian promoter" is capable of directing transcription of a polypeptide coding sequence operably linked to the promoter. The promoter should generally be active in T cells and antigen presenting cells and may be obtained from a gene that is expressed in T cells or antigen presenting cells. However, it need not be a T cell-specific or an antigen presenting cell specific-promoter. Instead, the promoter may be selected from any mammalian or viral promoter that can function in a T cell. Hence the promoter may be an actin promoter, an immunoglobulin promoter, a heat-shock promoter, or a viral promoter obtained from the genome of viruses such as adenoviruses, retroviruses, lentiviruses, herpes viruses, including but not limited to, polyoma virus, fowlpox virus, adenovirus 2, bovine papilloma virus, avian sarcoma virus, cytomegalovirus (CMV), hepatitis-B virus, Simian Virus 40 (SV40), Epstein Barr virus (EBV),

feline immunedeficiency virus (FIV), and Sr.alpha., or are respiratory synsitial viral promoters (RSV) or long terminal repeats (LTRs) of a retrovirus, i.e., a Moloney Murine Leukemia Virus (MoMuLv) (Cepko et al. (1984) Cell 37:1053-1062). The promoter functional in a mammalian cell can be inducible or constitutive.

Any cloning procedure used by one of skill in the art can be employed to make the expression vectors or expression that comprise a promoter operably linked to a CD83 nucleic acid, CD83 transcription factor or a nucleic acid encoding an anti-CD83 antibody. *See, e.g.,* Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y., 1989; Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y., 2001.

After constructing an expression vector or an expression cassette encoding CD83 gene products, CD83 transcription factors, CD83 anti-sense nucleic acid, intracellular antibodies capable of binding to CD83 or dominant negative CD83 inhibitors, mammalian cells can be transformed with the vector or cassette. Examples of such methods include:

Direct Injection: Naked DNA can be introduced into cells in vivo by directly injecting the DNA into the cells (see e.g., Acsadi et al. (1991) Nature 332:815-818; Wolff et al. (1990) Science 247:1465-1468). For example, a delivery apparatus (e.g., a "gene gun") for injecting DNA into cells in vivo can be used. Such an apparatus is commercially available (e.g., from BioRad).

Receptor-Mediated DNA Uptake: Naked DNA can also be introduced into cells in vivo by complexing the DNA to a cation, such as polylysine, which is coupled to a ligand for a cell-surface receptor (see for example Wu, G. and Wu, C. H. (1988) J. Biol. Chem. 263:14621; Wilson et al. (1992) J. Biol. Chem. 267:963-967; and U.S. Pat. No. 5,166,320). Binding of the DNA-ligand complex to the receptor facilitates uptake of the DNA by receptor-mediated endocytosis. A DNA-ligand complex linked to adenovirus capsids that naturally disrupt endosomes, thereby releasing material into the cytoplasm can be used to avoid degradation of the complex by intracellular lysosomes (see for example Curiel et al. (1991) Proc. Natl. Acad Sci. USA 88:8850; Cristiano et al. (1993) Proc. Natl. Acad. Sci. USA 90:2122-2126).

Retroviruses: Defective retroviruses are well characterized for use in gene transfer for gene therapy purposes (for a review see Miller, A. D. (1990) Blood 76:271). A recombinant retrovirus can be constructed having nucleotide sequences of interest incorporated into the retroviral genome. Additionally, portions of the retroviral genome can be removed to render the retrovirus replication defective. The replication defective retrovirus is then packaged into virions that can be used to infect a target cell through the use of a helper virus by standard techniques. Protocols for producing recombinant retroviruses and for infecting cells in vitro or in vivo with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, F. M. et al. (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14 and other standard laboratory manuals. Examples of suitable retroviruses include pLJ, pZIP, pWE and pEM which are available to those skilled in the art. Examples of suitable packaging virus lines include ΨCrip, ΨCre, Ψ2 and ΨAm. Retroviruses have been used to introduce a variety of genes into many different cell types, including epithelial cells, endothelial cells, lymphocytes, myoblasts, hepatocytes, bone marrow cells, in vitro and/or in vivo (see for example Eglitis, et al. (1 985) Science 230:1395-1398; Danos and Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:6460-6464; Wilson et al. (1 988) Proc. Natl. Acad. Sci. USA 85:3014-3018; Armentano et al. (1990) Proc. Natl. Acad. Sci. USA 87:6141-6145; Huber et al. (1991) Proc. Natl. Acad. Sci. USA 88:8039-8043; Ferry et al. (1991) Proc. Natl. Acad. Sci. USA 88:8377-8381; Chowdhury et al. (1991) Science 254:1802-1805; van Beusechem et al. (1992) Proc. Natl. Acad. Sci. USA 89:7640-7644; Kay et al. (1992) Human Gene Therapy 3:641-647; Dai et al. (1992) Proc. Natl. Acad. Sci USA 89:10892-10895; Hwu et al. (1993) J. Immunol. 150:4104-4115; U.S. Pat. Nos. 4,868,116; 4,980,286; PCT Application WO 89/07136; PCT Application WO 89/02468; PCT Application WO 89/05345; and PCT Application WO 92/07573). Retroviral vectors require target cell division in order for the retroviral genome (and foreign nucleic acid inserted into it) to be integrated into the host genome to stably introduce nucleic acid into the cell. Thus, it may be necessary to stimulate replication of the target cell.

Adenoviruses: The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms

of its ability to replicate in a normal lytic viral life cycle. See, for example, Berkner et al. (1988) BioTechniques 6:616; Rosenfeld et al. (1991) Science 252:431-434; and Rosenfeld et al. (1992) Cell 68:143-155. Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are available to those skilled in the art. Recombinant adenoviruses are advantageous in that they do not require dividing cells to be effective gene delivery vehicles and can be used to infect a wide variety of cell types, including airway epithelium (Rosenfeld et al. (1992) cited supra), endothelial cells (Lemarchand et al. (1992) Proc. Natl. Acad. Sci. USA 89:6482-6486), hepatocytes (Herz and Gerard (1993) Proc. Natl. Acad Sci. USA 90:2812-2816) and muscle cells (Quantin et al. (1992) Proc. Natl. Acad. Sci. USA 89:2581-2584). Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis in situations where introduced DNA becomes integrated into the host genome (e.g., retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors (Berkner et al. cited supra; Haj-Ahmand and Graham (1986) J. Virol. 57:267). Most replication-defective adenoviral vectors currently in use are deleted for all or parts of the viral E1 and E3 genes but retain as much as 80% of the adenoviral genetic material.

Adeno-Associated Viruses: Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka et al. Curr. Topics in Micro. and Immunol. (1992) 158:97-129). It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration (see for example Flotte et al. (1992) Am. J. Respir. Cell. Mol. Biol. 7:349-356; Samulski et al. (1989) J. Virol. 63:3822-3828; and McLaughlin et al. (1989) J. Virol. 62:1963-1973). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous DNA is limited to about 4.5 kb. An AAV vector such as that described in Tratschin et al. (1985) Mol. Cell. Biol. 5:3251-3260 can be used to introduce DNA into cells. A variety of nucleic

acids have been introduced into different cell types using AAV vectors (see for example Hermonat et al. (1984) Proc. Natl. Acad. Sci. USA 81:6466-6470; Tratschin et al. (1985) Mol. Cell. Biol. 4:2072-2081; Wondisford et al. (1988) Mol. Endocrinol. 2:32-39; Tratschin et al. (1984) J Virol. 51:611-619; and Flotte et al. (1993) J. Biol. Chem. 268:3781-3790).

Transformed mammalian cells can then be identified and administered to the mammal from whence they came to permit expression of a CD83 gene product, CD83 transcription factor, CD83 anti-sense nucleic acid, intracellular antibody capable of binding to CD83 proteins, or dominant negative CD83 inhibitors. The efficacy of a particular expression vector system and method of introducing nucleic acid into a cell can be assessed by standard approaches routinely used in the art. For example, DNA introduced into a cell can be detected by a filter hybridization technique (e.g., Southern blotting). RNA produced by transcription of an introduced DNA can be detected, for example, by Northern blotting, RNase protection or reverse transcriptase-polymerase chain reaction (RT-PCR). The CD83 gene product can be detected by an appropriate assay, for example, by immunological detection of a produced CD83 protein, such as with a CD83-specific antibody.

CD83 Antibodies

The invention provides antibody preparations directed against the mutant and wild type CD83 polypeptides of the invention, for example, against a polypeptide having SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9. Other antibodies of interest can bind to the cytoplasmic tail of CD83.

In one embodiment, the invention provides antibodies that block the function of CD83 polypeptides. Such antibodies may be used as CD83 inhibitory agents in the methods of the invention as described herein. In another embodiment, the antibodies of the invention can activate CD83 activity. Such activating antibodies may be used as CD83 stimulatory agents.

All antibody molecules belong to a family of plasma proteins called immunoglobulins, whose basic building block, the immunoglobulin fold or domain, is used in various forms in many molecules of the immune system and

other biological recognition systems. A typical immunoglobulin has four polypeptide chains, containing an antigen binding region known as a variable region and a non-varying region known as the constant region.

Native antibodies and immunoglobulins are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light and heavy chain variable domains (Clothia et al., J. Mol. Biol. 186, 651-66, 1985); Novotny and Haber, Proc. Natl. Acad. Sci. USA 82, 4592-4596 (1985).

Depending on the amino acid sequences of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are at least five (5) major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG-1, IgG-2, IgG-3 and IgG-4; IgA-1 and IgA-2. The heavy chains constant domains that correspond to the different classes of immunoglobulins are called alpha (α), delta (δ), epsilon (ϵ), gamma (γ) and mu (μ), respectively. The light chains of antibodies can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino sequences of their constant domain. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "variable" in the context of variable domain of antibodies, refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies. The variable domains are for binding and determine the specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed through the variable domains

of antibodies. It is concentrated in three segments called complementarity determining regions (CDRs) also known as hypervariable regions both in the light chain and the heavy chain variable domains.

The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies. The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector function, such as participation of the antibody in antibody-dependent cellular toxicity.

An antibody that is contemplated for use in the present invention thus can be in any of a variety of forms, including a whole immunoglobulin, an antibody fragment such as Fv, Fab, and similar fragments, a single chain antibody that includes the variable domain complementarity determining regions (CDR), and the like forms, all of which fall under the broad term "antibody," as used herein. The present invention contemplates the use of any specificity of an antibody, polyclonal or monoclonal, and is not limited to antibodies that recognize and immunoreact with a specific antigen. In preferred embodiments, in the context of both the therapeutic and screening methods described below, an antibody or fragment thereof is used that is immunospecific for an antigen or epitope of the invention.

The term "antibody fragment" refers to a portion of a full-length antibody, generally the antigen binding or variable region. Examples of antibody fragments include Fab, Fab', $F(ab')_2$ and Fv fragments. Papain digestion of antibodies produces two identical antigen binding fragments, called the Fab fragment, each with a single antigen binding site, and a residual "Fc" fragment, so-called for its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen binding fragments, which are capable of cross-linking antigen, and a residual other fragment (which is termed pFc'). Additional fragments can include diabodies, linear antibodies, single-chain antibody

molecules, and multispecific antibodies formed from antibody fragments. As used herein, "functional fragment" with respect to antibodies, refers to Fv, F(ab) and $F(ab')_2$ fragments.

Antibody fragments retain some ability to selectively bind with its antigen or receptor and are defined as follows:

(1) Fab is the fragment that contains a monovalent antigen-binding fragment of an antibody molecule. A Fab fragment can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain.

(2) Fab' is the fragment of an antibody molecule can be obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain. Two Fab' fragments are obtained per antibody molecule. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region.

(3) $(Fab')_2$ is the fragment of an antibody that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction. $F(ab')_2$ is a dimer of two Fab' fragments held together by two disulfide bonds.

(4) Fv is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in a tight, non-covalent association (V_H -V_L dimer). It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the V_H -V_L dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

(5) Single chain antibody ("SCA"), defined as a genetically engineered molecule containing the variable region of the light chain, the variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. Such single chain antibodies are also referred to as "single-chain Fv" or "sFv" antibody fragments. Generally, the Fv polypeptide further comprises a polypeptide linker between the VH and VL

domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, N.Y., pp. 269-315 (1994).

The term "diabodies" refers to a small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain (VH-VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161, and Hollinger et al., Proc. Natl. Acad Sci. USA 90: 6444-6448 (1993).

The preparation of polyclonal antibodies is well-known to those skilled in the art. See, for example, Green, et al., Production of Polyclonal Antisera, in: Immunochemical Protocols (Manson, ed.), pages 1-5 (Humana Press); Coligan, et al., Production of Polyclonal Antisera in Rabbits, Rats Mice and Hamsters, in: Current Protocols in Immunology, section 2.4.1 (1992), which are hereby incorporated by reference.

The preparation of monoclonal antibodies likewise is conventional. See, for example, Kohler & Milstein, Nature, 256:495 (1975); Coligan, et al., sections 2.5.1-2.6.7; and Harlow, et al., in: Antibodies: A Laboratory Manual, page 726 (Cold Spring Harbor Pub. (1988)), which are hereby incorporated by reference. Methods of *in vitro* and *in vivo* manipulation of monoclonal antibodies are also available to those skilled in the art. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein, Nature 256, 495 (1975), or may be made by recombinant methods, e.g., as described in U.S. Patent No. 4,816,567. The monoclonal antibodies for use with the present invention may also be isolated from antibody libraries using the techniques described in Clackson et al. Nature 352: 624-628 (1991), as well as in Marks et al., J. Mol Biol. 222: 581-597 (1991).

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques

include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography. See, e.g., Coligan, et al., sections 2.7.1-2.7.12 and sections 2.9.1-2.9.3; Barnes, et al., Purification of Immunoglobulin G (IgG), in: Methods in Molecular Biology, Vol. 10, pages 79-104 (Humana Press (1992).

Another method for generating antibodies involves a Selected Lymphocyte Antibody Method (SLAM). The SLAM technology permits the generation, isolation and manipulation of monoclonal antibodies without the process of hybridoma generation. The methodology principally involves the growth of antibody forming cells, the physical selection of specifically selected antibody forming cells, the isolation of the genes encoding the antibody and the subsequent cloning and expression of those genes.

More specifically, an animal (rabbit, mouse, rat, other) is immunized with a source of specific antigen. This immunization may consist of purified protein, in either native or recombinant form, peptides, DNA encoding the protein of interest or cells expressing the protein of interest. After a suitable period, during which antibodies can be detected in the serum of the animal (usually weeks to months), blood (or other tissue) from the animal is harvested. Lymphocytes are isolated from the blood and cultured under specific conditions to generate antibody-forming cells, with antibody being secreted into the culture medium. These cells are detected by any of several means (complement mediated lysis of antigen-bearing cells, fluorescence detection or other) and then isolated using micromanipulation technology. The individual antibody forming cells are then processed for eventual single cell PCR to obtain the expressed Heavy and Light chain genes that encode the specific antibody. Once obtained and sequenced, these genes are cloned into an appropriate expression vector and recombinant, monoclonal antibody produced in a heterologous cell system. These antibodies are then purified via standard methodologies such as the use of protein A affinity columns. These types of methods are further described in Babcook, et al., Proc. Natl. Acad. Sci. (USA) **93:** 7843-7848 (1996); U.S. Patent No. 5,627,052; and PCT WO 92/02551 by Schrader.

Another method involves humanizing a monoclonal antibody by recombinant means to generate antibodies containing human specific and

recognizable sequences. See, for review, Holmes, et al., J. Immunol., 158:2192-2201 (1997) and Vaswani, et al., Annals Allergy, Asthma & Immunol., 81:105-115 (1998). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In additional to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the antibody is obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567); Morrison et al. Proc. Natl. Acad Sci. 81, 6851-6855 (1984).

Methods of making antibody fragments are also known in the art (see for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York, (1988), incorporated herein by reference). Antibody fragments of the present invention can be prepared by proteolytic hydrolysis of the antibody or by expression in *E. coli* of DNA encoding the fragment. Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S

fragment denoted $F(ab')_2$. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulfhydryl groups resulting from cleavage of disulfide linkages, to produce 3.5S Fab= monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two monovalent Fab' fragments and an Fc fragment directly. These methods are described, for example, in U.S. Patents No. 4,036,945 and No. 4,331,647, and references contained therein. These patents are hereby incorporated in their entireties by reference.

Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical, or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody. For example, Fv fragments comprise an association of V_H and V_L chains. This association may be noncovalent or the variable chains can be linked by an intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde. Preferably, the Fv fragments comprise V_H and V_L chains connected by a peptide linker. These single-chain antigen binding proteins (sFv) are prepared by constructing a structural gene comprising DNA sequences encoding the V_H and V_L domains connected by an oligonucleotide. The structural gene is inserted into an expression vector, which is subsequently introduced into a host cell such as *E. coli*. The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Methods for producing sFvs are described, for example, by Whitlow, et al., Methods: a Companion to Methods in Enzymology, Vol. 2, page 97 (1991); Bird, et al., Science 242:423-426 (1988); Ladner, et al, US Patent No. 4,946,778; and Pack, et al., Bio/Technology 11:1271-77 (1993).

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells. See, for example, Larrick, et al., Methods: a Companion to Methods in Enzymology, Vol. 2, page 106 (1991).

The invention further contemplates human and humanized forms of non-human (e.g. murine) antibodies. Such humanized antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a nonhuman species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity.

In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance. In general, humanized antibodies can comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the Fv regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see: Jones et al., Nature 321, 522-525 (1986); Reichmann et al., Nature 332, 323-329 (1988); Presta, Curr. Op. Struct. Biol. 2, 593-596 (1992); Holmes, et al., J. Immunol., 158:2192-2201 (1997) and Vaswani, et al., Annals Allergy, Asthma & Immunol., 81:105-115 (1998).

The invention also provides methods of mutating antibodies to optimize their affinity, selectivity, binding strength or other desirable property. A mutant antibody refers to an amino acid sequence variant of an antibody. In general, one or more of the amino acid residues in the mutant antibody is different from what is present in the reference antibody. Such mutant antibodies necessarily have less than 100% sequence identity or similarity with the reference amino acid sequence. In general, mutant antibodies have at least 75% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the reference antibody. Preferably, mutant antibodies

have at least 80%, more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the reference antibody.

The antibodies of the invention are isolated antibodies. An isolated antibody is one that has been identified and separated and/or recovered from a component of the environment in which it was produced. Contaminant components of its production environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. The term "isolated antibody" also includes antibodies within recombinant cells because at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

If desired, the antibodies of the invention can be purified by any available procedure. For example, the antibodies can be affinity purified by binding an antibody preparation to a solid support to which the antigen used to raise the antibodies is bound. After washing off contaminants, the antibody can be eluted by known procedures. Those of skill in the art will know of various techniques common in the immunology arts for purification and/or concentration of polyclonal antibodies, as well as monoclonal antibodies (see for example, Coligan, et al., Unit 9, Current Protocols in Immunology, Wiley Interscience, 1991, incorporated by reference).

In preferred embodiments, the antibody will be purified as measurable by at least three different methods: 1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight; 2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequentator; or 3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomasie blue or, preferably, silver stain.

The invention also provides antibodies that can bind to CD83 polypeptides. Sequences of complementarity determining regions (CDRs) or hypervariable regions from light and heavy chains of these anti-CD83 antibodies

are provided. For example, a heavy chain variable region having a CDR1 sequence of SYDMT (SEQ ID NO:23), SYDMS (SEQ ID NO:24), DYDLS (SEQ ID NO:25) or SYDMS (SEQ ID NO:26) can be used in an antibody or other binding moiety to bind to CD83 gene products. In other embodiments, a heavy chain variable region having a CDR2 sequence of YASGSTYY (SEQ ID NO:27), SSSGTTYY (SEQ ID NO:28), YASGSTYY (SEQ ID NO:29), AIDGNPYY (SEQ ID NO:30) or STAYNSHY (SEQ ID NO:31) can be used in an antibody or other binding moiety to bind to CD83 gene products. In further embodiments of the invention, a heavy chain variable region having a CDR3 sequence of EHAGYSGDTGH (SEQ ID NO:32), EGAGVSMT (SEQ ID NO:33), EDAGFSNA (SEQ ID NO:34), GAGD (SEQ ID NO:35) or GGSWLD (SEQ ID NO:36) can be used in an antibody or other binding moiety to bind to CD83 gene products.

Moreover, a light chain variable region having a CDR1 sequence of RCAYD (SEQ ID NO:37), RCADVV (SEQ ID NO:38), or RCALV (SEQ ID NO:39) can be used in an antibody or other binding moiety to bind to CD83 gene products. In other embodiments, a light chain variable region having a CDR2 sequence of QSISTY (SEQ ID NO:40), QSVSSY (SEQ ID NO:41), ESISNY (SEQ ID NO:42), KNVYNNNW (SEQ ID NO:43), or QSVYDNDE (SEQ ID NO:43) can be used in an antibody or other binding moiety to bind to CD83 gene products. In further embodiments, a light chain variable region having a CDR3 sequence of QQGYTHSNVDNV (SEQ ID NO:44), QQGYSISDIDNA (SEQ ID NO:45), QCTSGGKFISDGAA (SEQ ID NO:46), AGDYSSSSDNG (SEQ ID NO:47), or QATHYSSDWLTY (SEQ ID NO:48) can be used in an antibody or other binding moiety to bind to CD83 gene products.

Light and heavy chains that can bind CD83 polypeptides are also provided by the invention. For example, in one embodiment, the invention provides a 20D04 light chain that can bind to CD83 polypeptides. The amino acid sequence for this 20D04 light chain is provided below (SEQ ID NO:11).

```
  1 MDMRAPTQLL GLLLLWLPGA RCADVVMTQT PASVSAAVGG
 41 TVTINCQASE SISNYLSWYQ QKPGQPPKLL IYRTSTLASG
 81 VSSRFKGSGS GTEYTLTISG VQCDDVATYY CQCTSGGKFI
121 SDGAAFGGGT EVVVKGDPVA PTVLLFPPSS DEVATGTVTI
161 VCVANKYFPD VTVTWEVDGT TQTTGIENSK TPQNSADCTY
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201 NLSSTLTLTS TQYNSHKEYT CKVTQGTTSV VQSFSRKNC

A nucleic acid sequence for this 20D04 anti-CD83 light chain is provided below (SEQ ID NO:12).

```
  1 ATGGACATGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
 41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCG ATGTCGTGAT
 81 GACCCAGACT CCAGCCTCCG TGTCTGCAGC TGTGGGAGGC
121 ACAGTCACCA TCAATTGCCA GGCCAGTGAA AGCATTAGCA
161 ACTACTTATC CTGGTATCAG CAGAAACCAG GGCAGCCTCC
201 CAAGCTCCTG ATCTACAGGA CATCCACTCT GGCATCTGGG
241 GTCTCATCGC GGTTCAAAGG CAGTGGATCT GGGACAGAGT
281 ACACTCTCAC CATCAGCGGC GTGCAGTGTG ACGATGTTGC
321 CACTTACTAC TGTCAATGCA CTTCTGGTGG GAAGTTCATT
361 AGTGATGGTG CTGCTTTCGG CGGAGGGACC GAGGTGGTGG
401 TCAAAGGTGA TCCAGTTGCA CCTACTGTCC TCCTCTTCCC
441 ACCATCTAGC GATGAGGTGG CAACTGGAAC AGTCACCATC
481 GTGTGTGTGG CGAATAAATA CTTTCCCGAT GTCACCGTCA
521 CCTGGGAGGT GGATGGCACC ACCCAAACAA CTGGCATCGA
561 GAACAGTAAA ACACCGCAGA ATTCTGCAGA TTGTACCTAC
601 AACCTCAGCA GCACTCTGAC ACTGACCAGC ACACAGTACA
641 ACAGCCACAA AGAGTACACC TGCAAGGTGA CCCAGGGCAC
681 GACCTCAGTC GTCCAGAGCT TCAGTAGGAA GAACTGTTAA
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In another embodiment, the invention provides a 20D04 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 20D04 heavy chain is provided below (SEQ ID NO:13).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
 41 TVSGFSLSNN AINWVRQAPG KGLEWIGYIW SGGLTYYANW
 81 AEGRFTISKT STTVDLKMTS PTIEDTATYF CARGINNSAL
121 WGPGTLVTVS SGQPKAPSVF PLAPCCGDTP SSTVTLGCLV
161 KGYLPEPVTV TWNSGTLTNG VRTFPSVRQS SGLYSLSSVV
201 SVTSSSQPVT CNVAHPATNT KVDKTVAPST CSKPTCPPPE
241 LLGGPSVFIF PPKPKDTLMI SRTPEVTCVV VDVSQDDPEV
281 QFTWYINNEQ VRTARPPLRE QQFNSTIRVV STLPIAHQDW
321 LRGKEFKCKV HNKALPAPIE KTISKARGQP LEPKVYTMGP
361 PREELSSRSV SLTCMINGFY PSDISVEWEK NGKAEDNYKT
401 TPAVLDSDGS YFLYNKLSVP TSEWQRGDVF TCSVMHEALH
441 NHYTQKSISR SPGK
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A nucleic acid sequence for this 20D04 anti-CD83 heavy chain is provided below (SEQ ID NO:14).

```
   1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
  41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
  81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
 121 ACCGTCTCTG GATTCTCCCT CAGTAACAAT GCAATAAACT
 161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTAG AGTGGATCGG
 201 ATACATTTGG AGTGGTGGGC TTACATACTA CGCGAACTGG
 241 GCGGAAGGCC GATTCACCAT CTCCAAAACC TCGACTACGG
 281 TGGATCTGAA GATGACCAGT CCGACAATCG AGGACACGGC
 321 CACCTATTTC TGTGCCAGAG GGATTAATAA CTCCGCTTTG
 361 TGGGGCCCAG GCACCCTGGT CACCGTCTCC TCAGGGCAAC
 401 CTAAGGCTCC ATCAGTCTTC CCACTGGCCC CCTGCTGCGG
 441 GGACACACCC TCTAGCACGG TGACCTTGGG CTGCCTGGTC
 481 AAAGGCTACC TCCCGGAGCC AGTGACCGTG ACCTGGAACT
 521 CGGGCACCCT CACCAATGGG GTACGCACCT TCCCGTCCGT
 561 CCGGCAGTCC TCAGGCCTCT ACTCGCTGAG CAGCGTGGTG
 601 AGCGTGACCT CAAGCAGCCA GCCCGTCACC TGCAACGTGG
 641 CCCACCCAGC CACCAACACC AAAGTGGACA AGACCGTTGC
 681 GCCCTCGACA TGCAGCAAGC CCACGTGCCC ACCCCCTGAA
 721 CTCCTGGGGG GACCGTCTGT CTTCATCTTC CCCCCAAAAC
 761 CCAAGGACAC CCTCATGATC TCACGCACCC CCGAGGTCAC
 801 ATGCGTGGTG GTGGACGTGA GCCAGGATGA CCCCGAGGTG
 841 CAGTTCACAT GGTACATAAA CAACGAGCAG GTGCGCACCG
 881 CCCGGCCGCC GCTACGGGAG CAGCAGTTCA ACAGCACGAT
 921 CCGCGTGGTC AGCACCCTCC CCATCGCGCA CCAGGACTGG
 961 CTGAGGGGCA AGGAGTTCAA GTGCAAAGTC CACAACAAGG
1001 CACTCCCGGC CCCCATCGAG AAAACCATCT CCAAAGCCAG
1041 AGGGCAGCCC CTGGAGCCGA AGGTCTACAC CATGGGCCCT
1081 CCCCGGGAGG AGCTGAGCAG CAGGTCGGTC AGCCTGACCT
1121 GCATGATCAA CGGCTTCTAC CCTTCCGACA TCTCGGTGGA
1161 GTGGGAGAAG AACGGGAAGG CAGAGGACAA CTACAAGACC
1201 ACGCCGGCCG TGCTGGACAG CGACGGCTCC TACTTCCTCT
1241 ACAACAAGCT CTCAGTGCCC ACGAGTGAGT GGCAGCGGGG
1281 CGACGTCTTC ACCTGCTCCG TGATGCACGA GGCCTTGCAC
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1321 AACCACTACA CGCAGAAGTC CATCTCCCGC TCTCCGGGTA
1361 AA

In another embodiment, the invention provides a 11G05 light chain that can bind to CD83 polypeptides. The amino acid sequence for this 11G05 light chain is provided below (SEQ ID NO:15).

1 MDTRAPTQLL GLLLLWLPGA RCADVVMTQT PASVSAAVGG
41 TVTINCQSSK NVYNNNWLSW FQQKPGQPPK LLIYYASTLA
81 SGVPSRFRGS GSGTQFTLTI SDVQCDDAAT YYCAGDYSSS
121 SDNGFGGGTE VVVKGDPVAP TVLLFPPSSD EVATGTVTIV
161 CVANKYFPDV TVTWEVDGTT QTTGIENSKT PQNSADCTYN
201 LSSTLTLTST QYNSHKEYTC KVTQGTTSVV QSFSRKNC

A nucleic acid sequence for this 11G05 anti-CD83 light chain is provided below (SEQ ID NO:16).

1 ATGGACACCA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCG ACGTCGTGAT
81 GACCCAGACT CCAGCCTCCG TGTCTGCAGC TGTGGGAGGC
121 ACAGTCACCA TCAATTGCCA GTCCAGTAAG AATGTTTATA
161 ATAACAACTG GTTATCCTGG TTTCAGCAGA AACCAGGGCA
201 GCCTCCCAAG CTCCTGATCT ATTATGCATC CACTCTGGCA
241 TCTGGGGTCC CATCGCGGTT CAGAGGCAGT GGATCTGGGA
281 CACAGTTCAC TCTCACCATT AGCGACGTGC AGTGTGACGA
321 TGCTGCCACT TACTACTGTG CAGGCGATTA TAGTAGTAGT
361 AGTGATAATG GTTTCGGCGG AGGGACCGAG GTGGTGGTCA
401 AAGGTGATCC AGTTGCACCT ACTGTCCTCC TCTTCCCACC
441 ATCTAGCGAT GAGGTGGCAA CTGGAACAGT CACCATCGTG
481 TGTGTGGCGA ATAAATACTT TCCCGATGTC ACCGTCACCT
521 GGGAGGTGGA TGGCACCACC CAAACAACTG GCATCGAGAA
561 CAGTAAAACA CCGCAGAATT CTGCAGATTG TACCTACAAC
601 CTCAGCAGCA CTCTGACACT GACCAGCACA CAGTACAACA
641 GCCACAAAGA GTACACCTGC AAGGTGACCC AGGGCACGAC
681 CTCAGTCGTC CAGAGCTTCA GTAGGAAGAA CTGTTAA

In another embodiment, the invention provides a 11G05 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 11G05 heavy chain is provided below (SEQ ID NO:17).

1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
41 TVSGFTISDY DLSWVRQAPG EGLKYIGFIA IDGNPYYATW

81 AKGRFTISKT STTVDLKITA PTTEDTATYF CARGAGDLWG
121 PGTLVTVSSG QPKAPSVFPL APCCGDTPSS TVTLGCLVKG
161 YLPEPVTVTW NSGTLTNGVR TFPSVRQSSG LYSLSSVVSV
201 TSSSQPVTCN VAHPATNTKV DKTVAPSTCS KPTCPPPELL
241 GGPSVFIFPP KPKDTLMISR TPEVTCVVVD VSQDDPEVQF
281 TWYINNEQVR TARPPLREQQ FNSTIRVVST LPIAHQDWLR
321 GKEFKCKVHN KALPAPIEKT ISKARGQPLE PKVYTMGPPR
361 EELSSRSVSL TCMINGFYPS DISVEWEKNG KAEDNYKTTP
401 AVLDSDGSYF LYNKLSVPTS EWQRGDVFTC SVMHEALHNH
441 YTQKSISRSP GK

A nucleic acid sequence for this 11G05 anti-CD83 heavy chain is provided below (SEQ ID NO:18).

1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGTCTCTG GATTCACCAT CAGTGACTAC GACTTGAGCT
161 GGGTCCGCCA GGCTCCAGGG GAGGGGCTGA AATACATCGG
201 ATTCATTGCT ATTGATGGTA ACCCATACTA CGCGACCTGG
241 GCAAAAGGCC GATTCACCAT CTCCAAAACC TCGACCACGG
281 TGGATCTGAA AATCACCGCT CCGACAACCG AAGACACGGC
321 CACGTATTTC TGTGCCAGAG GGGCAGGGGA CCTCTGGGGC
361 CCAGGGACCC TCGTCACCGT CTCTTCAGGG CAACCTAAGG
401 CTCCATCAGT CTTCCCACTG GCCCCCTGCT GCGGGGACAC
441 ACCCTCTAGC ACGGTGACCT TGGGCTGCCT GGTCAAAGGC
481 TACCTCCCGG AGCCAGTGAC CGTGACCTGG AACTCGGGCA
521 CCCTCACCAA TGGGGTACGC ACCTTCCCGT CCGTCCGGCA
561 GTCCTCAGGC CTCTACTCGC TGAGCAGCGT GGTGAGCGTG
601 ACCTCAAGCA GCCAGCCCGT CACCTGCAAC GTGGCCCACC
641 CAGCCACCAA CACCAAAGTG GACAAGACCG TTGCGCCCTC
681 GACATGCAGC AAGCCCACGT GCCCACCCCC TGAACTCCTG
721 GGGGGACCGT CTGTCTTCAT CTTCCCCCCA AAACCCAAGG
761 ACACCCTCAT GATCTCACGC ACCCCCGAGG TCACATGCGT
801 GGTGGTGGAC GTGAGCCAGG ATGACCCCGA GGTGCAGTTC
841 ACATGGTACA TAAACAACGA GCAGGTGCGC ACCGCCCGGC

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 881 CGCCGCTACG GGAGCAGCAG TTCAACAGCA CGATCCGCGT
 921 GGTCAGCACC CTCCCCATCG CGCACCAGGA CTGGCTGAGG
 961 GGCAAGGAGT TCAAGTGCAA AGTCCACAAC AAGGCACTCC
1001 CGGCCCCCAT CGAGAAAACC ATCTCCAAAG CCAGAGGGCA
1041 GCCCCTGGAG CCGAAGGTCT ACACCATGGG CCCTCCCCGG
1081 GAGGAGCTGA GCAGCAGGTC GGTCAGCCTG ACCTGCATGA
1120 TCAACGGCTT CTACCCTTCC GACATCTCGG TGGAGTGGGA
1161 GAAGAACGGG AAGGCAGAGG ACAACTACAA GACCACGCCG
1201 GCCGTGCTGG ACAGCGACGG CTCCTACTTC CTCTACAACA
1241 AGCTCTCAGT GCCCACGAGT GAGTGGCAGC GGGGCGACGT
1281 CTTCACCTGC TCCGTGATGC ACGAGGCCTT GCACAACCAC
1321 TACACGCAGA AGTCCATCTC CCGCTCTCCG GGTAAA
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In another embodiment, the invention provides a 14C12 light chain that can bind to CD83 polypeptides. The amino acid sequence for this 14C12 light chain is provided below (SEQ ID NO:19).

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  1 MDXRAPTQLL GLLLLWLPGA RCALVMTQTP ASVSAAVGGT
 41 VTINCQSSQS VYDNDELSWY QQKPGQPPKL LIYLASKLAS
 81 GVPSRFKGSG SGTQFALTIS GVQCDDAATY YCQATHYSSD
121 WYLTFGGGTE VVVKGDPVAP TVLLFPPSSD EVATGTVTIV
161 CVANKYFPDV TVTWEVDGTT QTTGIENSKT PQNSADCTYN
201 LSSTLTLTST QYNSHKEYTC KVTQGTTSVV QSFSRKNC
```

A nucleic acid sequence for this 14C12 anti-CD83 light chain is provided below (SEQ ID NO:20).

```
  1 ATGGACATRA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
 41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCC TTGTGATGAC
 81 CCAGACTCCA GCCTCCGTGT CTGCAGCTGT GGGAGGCACA
121 GTCACCATCA ATTGCCAGTC CAGTCAGAGT GTTTATGATA
161 ACGACGAATT ATCCTGGTAT CAGCAGAAAC CAGGGCAGCC
201 TCCCAAGCTC CTGATCTATC TGGCATCCAA GTTGGCATCT
241 GGGGTCCCAT CCCGATTCAA AGGCAGTGGA TCTGGGACAC
281 AGTTCGCTCT CACCATCAGC GGCGTGCAGT GTGACGATGC
321 TGCCACTTAC TACTGTCAAG CCACTCATTA TAGTAGTGAT
361 TGGTATCTTA CTTTCGGCGG AGGGACCGAG GTGGTGGTCA
401 AAGGTGATCC AGTTGCACCT ACTGTCCTCC TCTTCCCACC
441 ATCTAGCGAT GAGGTGGCAA CTGGAACAGT CACCATCGTG
481 TGTGTGGCGA ATAAATACTT TCCCGATGTC ACCGTCACCT
521 GGGAGGTGGA TGGCACCACC CAAACAACTG GCATCGAGAA
561 CAGTAAAACA CCGCAGAATT CTGCAGATTG TACCTACAAC
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601 CTCAGCAGCA CTCTGACACT GACCAGCACA CAGTACAACA
641 GCCACAAAGA GTACACCTGC AAGGTGACCC AGGGCACGAC
681 CTCAGTCGTC CAGAGCTTCA GTAGGAAGAA CTGTTAA

In another embodiment, the invention provides a 14C12 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 14C12 heavy chain is provided below (SEQ ID NO:21).

1 METGLRWLLL VAVLKGVHCQ SVEESGGRLV TPGTPLTLTC
41 TASGFSRSSY DMSWVRQAPG KGLEWVGVIS TAYNSHYASW
81 AKGRFTISRT STTVDLKMTS LTTEDTATYF CARGGSWLDL
121 WGQGTLVTVS SGQPKAPSVF PLAPCCGDTP SSTVTLGCLV
161 KGYLPEPVTV TWNSGTLTNG VRTFPSVRQS SGLYSLSSVV
201 SVTSSSQPVT CNVAHPATNT KVDKTVAPST CSKPTCPPPE
241 LLGGPSVFIF PPKPKDTLMI SRTPEVTCVV VDVSQDDPEV
281 QFTWYINNEQ VRTARPPLRE QQFNSTIRVV STLPIAHQDW
321 LRGKEFKCKV HNKALPAPIE KTISKARGQP LEPKVYTMGP
361 PREELSSRSV SLTCMINGFY PSDISVEWEK NGKAEDNYKT
401 TPAVLDSDGS YFLYNKLSVP TSEWQRGDVF TCSVMHEALH
441 NHYTQKSISR SPGK

A nucleic acid sequence for this 14C12 anti-CD83 heavy chain is provided below (SEQ ID NO:22).

1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
41 TCAAAGGTGT CCACTGTCAG TCGGTGGAGG AGTCCGGGGG
81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGCCTCTG GATTCTCCCG CAGCAGCTAC GACATGAGCT
161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGGTCGG
201 AGTCATTAGT ACTGCTTATA ACTCACACTA CGCGAGCTGG
241 GCAAAAGGCC GATTCACCAT CTCCAGAACC TCGACCACGG
281 TGGATCTGAA AATGACCAGT CTGACAACCG AAGACACGGC
321 CACCTATTTC TGTGCCAGAG GGGGTAGTTG GTTGGATCTC
361 TGGGGCCAGG GCACCCTGGT CACCGTCTCC TCAGGGCAAC
401 CTAAGGCTCC ATCAGTCTTC CCACTGGCCC CCTGCTGCGG
441 GGACACACCC TCTAGCACGG TGACCTTGGG CTGCCTGGTC
481 AAAGGCTACC TCCCGGAGCC AGTGACCGTG ACCTGGAACT

```
 521 CGGGCACCCT CACCAATGGG GTACGCACCT TCCCGTCCGT
 561 CCGGCAGTCC TCAGGCCTCT ACTCGCTGAG CAGCGTGGTG
 601 AGCGTGACCT CAAGCAGCCA GCCCGTCACC TGCAACGTGG
 641 CCCACCCAGC CACCAACACC AAAGTGGACA AGACCGTTGC
 681 GCCCTCGACA TGCAGCAAGC CCACGTGCCC ACCCCCTGAA
 721 CTCCTGGGGG GACCGTCTGT CTTCATCTTC CCCCCAAAAC
 761 CCAAGGACAC CCTCATGATC TCACGCACCC CCGAGGTCAC
 801 ATGCGTGGTG GTGGACGTGA GCCAGGATGA CCCCGAGGTG
 841 CAGTTCACAT GGTACATAAA CAACGAGCAG GTGCGCACCG
 881 CCCGGCCGCC GCTACGGGAG CAGCAGTTCA ACAGCACGAT
 921 CCGCGTGGTC AGCACCCTCC CCATCGCGCA CCAGGACTGG
 961 CTGAGGGGCA AGGAGTTCAA GTGCAAAGTC CACAACAAGG
1001 CACTCCCGGC CCCCATCGAG AAAACCATCT CCAAAGCCAG
1041 AGGGCAGCCC CTGGAGCCGA AGGTCTACAC CATGGGCCCT
1081 CCCCGGGAGG AGCTGAGCAG CAGGTCGGTC AGCCTGACCT
1121 GCATGATCAA CGGCTTCTAC CCTTCCGACA TCTCGGTGGA
1161 GTGGGAGAAG AACGGGAAGG CAGAGGACAA CTACAAGACC
1200 ACGCCGGCCG TGCTGGACAG CGACGGCTCC TACTTCCTCT
1241 ACAACAAGCT CTCAGTGCCC ACGAGTGAGT GGCAGCGGGG
1281 CGACGTCTTC ACCTGCTCCG TGATGCACGA GGCCTTGCAC
1321 AACCACTACA CGCAGAAGTC CATCTCCCGC TCTCCGGGTA
1361 AA
```

In another embodiment, the invention provides a M83 020B08L light chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 020B08L light chain is provided below (SEQ ID NO:58).

```
  1 MDMRAPTQLL GLLLLWLPGA RCAYDMTQTP ASVEVAVGGT
 41 VTIKCQASQS ISTYLDWYQQ KPGQPPKLLI YDASDLASGV
 81 PSRFKGSGSG TQFTLTISDL ECADAATYYC QQGYTHSNVD
121 NVFGGGTEVV VKGDPVAPTV LLFPPSSDEV ATGTVTIVCV
161 ANKYFPDVTV TWEVDGTTQT TGIENSKTPQ NSADCTYNLS
201 STLTLTSTQY NSHKEYTCKV TQGTTSVVQS FSRKNC
```

A nucleic acid sequence for this M83 020B08L anti-CD83 light chain is provided below (SEQ ID NO:59).

```
  1 ATGGACATGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
 41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCT ATGATATGAC
 81 CCAGACTCCA GCCTCTGTGG AGGTAGCTGT GGGAGGCACA
121 GTCACCATCA AGTGCCAGGC CAGTCAGAGC ATTAGTACCT
161 ACTTAGACTG GTATCAGCAG AAACCAGGGC AGCCTCCCAA
201 GCTCCTGATC TATGATGCAT CCGATCTGGC ATCTGGGGTC
241 CCATCGCGGT TCAAAGGCAG TGGATCTGGG ACACAGTTCA
281 CTCTCACCAT CAGCGACCTG GAGTGTGCCG ATGCTGCCAC
321 TTACTACTGT CAACAGGGTT ATACACATAG TAATGTTGAT
361 AATGTTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAAGGTG
401 ATCCAGTTGC ACCTACTGTC CTCCTCTTCC CACCATCTAG
441 CGATGAGGTG GCAACTGGAA CAGTCACCAT CGTGTGTGTG
481 GCGAATAAAT ACTTTCCCGA TGTCACCGTC ACCTGGGAGG
521 TGGATGGCAC CACCCAAACA ACTGGCATCG AGAACAGTAA
561 AACACCGCAG AATTCTGCAG ATTGTACCTA CAACCTCAGC
601 AGCACTCTGA CACTGACCAG CACACAGTAC AACAGCCACA
641 AAGAGTACAC CTGCAAGGTG ACCCAGGGCA CGACCTCAGT
681 CGTCCAGAGC TTCAGTAGGA AGAACTGTTA A
```

In another embodiment, the invention provides a M83 020B08H heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 020B08H heavy chain is provided below (SEQ ID NO:60).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
 41 TVSGFSLSSY DMTWVRQAPG KGLEWIGIIY ASGTTYYANW
 81 AKGRFTISKT STTVDLKVTS PTIGDTATYF CAREGAGVSM
121 TLWGPGTLVT VSSGQPKAPS VFPLAPCCGD TPSSTVTLGC
161 LVKGYLPEPV TVTWNSGTLT NGVRTFPSVR QSSGLYSLSS
201 VVSVTSSSQP VTCNVAHPAT NTKVDKTVAP STCSKPTCPP
241 PELLGGPSVF IFPPKPKDTL MISRTPEVTC VVVDVSQDDP
281 EVQFTWYINN EQVRTARPPL REQQFNSTIR VVSTLPIAHQ
321 DWLRGKEFKC KVHNKALPAP IEKTISKARG QPLEPKVYTM
361 GPPREELSSR SVSLTCMING FYPSDISVEW EKNGKAEDNY
401 KTTPAVLDSD GSYFLYNKLS VPTSEWQRGD VFTCSVMHEA
441 LHNHYTQKSI SRSPGK
```

A nucleic acid sequence for this M83 020B08H anti-CD83 heavy chain is provided below (SEQ ID NO:61).

```
  1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
 41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
 81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGTCTCTG GATTCTCCCT CAGCAGCTAC GACATGACCT
161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGATCGG
201 AATCATTTAT GCTAGTGGTA CCACATACTA CGCGAACTGG
241 GCGAAAGGCC GATTCACCAT CTCCAAAACC TCGACCACGG
281 TGGATCTGAA AGTCACCAGT CCGACAATCG GGGACACGGC
321 CACCTATTTC TGTGCCAGAG AGGGGGCTGG TGTTAGTATG
361 ACCTTGTGGG GCCCAGGCAC CCTGGTCACC GTCTCCTCAG
401 GGCAACCTAA GGCTCCATCA GTCTTCCCAC TGGCCCCCTG
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 441 CTGCGGGGAC ACACCCTCTA GCACGGTGAC CTTGGGCTGC
 481 CTGGTCAAAG GCTACCTCCC GGAGCCAGTG ACCGTGACCT
 521 GGAACTCGGG CACCCTCACC AATGGGGTAC GCACCTTCCC
 561 GTCCGTCCGG CAGTCCTCAG GCCTCTACTC GCTGAGCAGC
 601 GTGGTGAGCG TGACCTCAAG CAGCCAGCCC GTCACCTGCA
 641 ACGTGGCCCA CCCAGCCACC AACACCAAAG TGGACAAGAC
 681 CGTTGCGCCC TCGACATGCA GCAAGCCCAC GTGCCCACCC
 721 CCTGAACTCC TGGGGGGACC GTCTGTCTTC ATCTTCCCCC
 761 CAAAACCCAA GGACACCCTC ATGATCTCAC GCACCCCCGA
 801 GGTCACATGC GTGGTGGTGG ACGTGAGCCA GGATGACCCC
 841 GAGGTGCAGT TCACATGGTA CATAAACAAC GAGCAGGTGC
 881 GCACCGCCCG GCCGCCGCTA CGGGAGCAGC AGTTCAACAG
 921 CACGATCCGC GTGGTCAGCA CCCTCCCCAT CGCGCACCAG
 961 GACTGGCTGA GGGGCAAGGA GTTCAAGTGC AAAGTCCACA
1001 ACAAGGCACT CCCGGCCCCC ATCGAGAAAA CCATCTCCAA
1041 AGCCAGAGGG CAGCCCCTGG AGCCGAAGGT CTACACCATG
1081 GGCCCTCCCC GGGAGGAGCT GAGCAGCAGG TCGGTCAGCC
1121 TGACCTGCAT GATCAACGGC TTCTACCCTT CCGACATCTC
1161 GGTGGAGTGG GAGAAGAACG GGAAGGCAGA GGACAACTAC
1201 AAGACCACGC CGGCCGTGCT GGACAGCGAC GGCTCCTACT
1241 TCCTCTACAA CAAGCTCTCA GTGCCCACGA GTGAGTGGCA
1281 GCGGGGCGAC GTCTTCACCT GCTCCGTGAT GCACGAGGCC
1321 TTGCACAACC ACTACACGCA GAAGTCCATC TCCCGCTCTC
1361 CGGGTAAA
```

In another embodiment, the invention provides a M83 006G05L light chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 006G05L light chain is provided below (SEQ ID NO:62).

```
  1 MDMRAPTQLL GLLLLWLPGA RCAYDMTQTP ASVEVAVGGT
 41 VAIKCQASQS VSSYLAWYQQ KPGQPPKPLI YEASMLAAGV
 81 SSRFKGSGSG TDFTLTISDL ECDDAATYYC QQGYSISDID
121 NAFGGGTEVV VKGDPVAPTV LLFPPSSDEV ATGTVTIVCV
161 ANKYFPDVTV TWEVDGTTQT TGIENSKTPQ NSADCTYNLS
201 STLTLTSTQY NSHKEYTCKV TQGTTSVVQS FSRKNC
```

A nucleic acid sequence for M83 006G05L anti-CD83 light chain is provided below (SEQ ID NO:63).

```
  1 ATGGACATGA GGGCCCCCAC TCAACTGCTG GGGCTCCTGC
 41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCT ATGATATGAC
 81 CCAGACTCCA GCCTCTGTGG AGGTAGCTGT GGGAGGCACA
121 GTCGCCATCA AGTGCCAGGC CAGTCAGAGC GTTAGTAGTT
161 ACTTAGCCTG GTATCAGCAG AAACCAGGGC AGCCTCCCAA
201 GCCCCTGATC TACGAAGCAT CCATGCTGGC GGCTGGGGTC
241 TCATCGCGGT TCAAAGGCAG TGGATCTGGG ACAGACTTCA
281 CTCTCACCAT CAGCGACCTG GAGTGTGACG ATGCTGCCAC
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321 TTACTATTGT CAACAGGGTT ATTCTATCAG TGATATTGAT
361 AATGCTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAAGGTG
401 ATCCAGTTGC ACCTACTGTC CTCCTCTTCC CACCATCTAG
441 CGATGAGGTG GCAACTGGAA CAGTCACCAT CGTGTGTGTG
481 GCGAATAAAT ACTTTCCCGA TGTCACCGTC ACCTGGGAGG
521 TGGATGGCAC CACCCAAACA ACTGGCATCG AGAACAGTAA
561 AACACCGCAG AATTCTGCAG ATTGTACCTA CAACCTCAGC
601 AGCACTCTGA CACTGACCAG CACACAGTAC AACAGCCACA
641 AAGAGTACAC CTGCAAGGTG ACCCAGGGCA CGACCTCAGT
681 CGTCCAGAGC TTCAGTAGGA AGAACTGTTA A
```

In another embodiment, the invention provides a M83 006G05L heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 006G05L heavy chain is provided below (SEQ ID NO:64).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV SPGTPLTLTC
 41 TASGFSLSSY DMSWVRQAPG KGLEYIGIIS SSGSTYYASW
 81 AKGRFTISKT STTVDLEVTS LTTEDTATYF CSREHAGYSG
121 DTGHLWGPGT LVTVSSGQPK APSVFPLAPC CGDTPSSTVT
161 LGCLVKGYLP EPVTVTWNSG TLTNGVRTFP SVRQSSGLYS
201 LSSVVSVTSS SQPVTCNVAH PATNTKVDKT VAPSTCSKPT
241 CPPPELLGGP SVFIFPPKPK DTLMISRTPE VTCVVVDVSQ
281 DDPEVQFTWY INNEQVRTAR PPLREQQFNS TIRVVSTLPI
321 AHQDWLRGKE FKCKVHNKAL PAPIEKTISK ARGQPLEPKV
361 YTMGPPREEL SSRSVSLTCM INGFYPSDIS VEWEKNGKAE
401 DNYKTTPAVL DSDGSYFLYN KLSVPTSEWQ RGDVFTCSVM
441 HEALHNHYTQ KSISRSPGK
```

A nucleic acid sequence for this M83 006G05L anti-CD83 heavy chain is provided below (SEQ ID NO:65).

```
  1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
 41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
 81 TCGCCTGGTC TCGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGCCTCTG GATTCTCCCT CAGTAGCTAC GACATGAGCT
161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATACATCGG
201 AATCATTAGT AGTAGTGGTA GCACATACTA CGCGAGCTGG
241 GCGAAAGGCC GATTCACCAT CTCCAAAACC TCGACCACGG
281 TGGATCTGGA AGTGACCAGT CTGACAACCG AGGACACGGC
321 CACCTATTTC TGTAGTAGAG AACATGCTGG TTATAGTGGT
361 GATACGGGTC ACTTGTGGGG CCCAGGCACC CTGGTCACCG
401 TCTCCTCGGG GCAACCTAAG GCTCCATCAG TCTTCCCACT
441 GGCCCCCTGC TGCGGGGACA CACCCTCTAG CACGGTGACC
481 TTGGGCTGCC TGGTCAAAGG CTACCTCCCG GAGCCAGTGA
521 CCGTGACCTG GAACTCGGGC ACCCTCACCA ATGGGGTACG
561 CACCTTCCCG TCCGTCCGGC AGTCCTCAGG CCTCTACTCG
601 CTGAGCAGCG TGGTGAGCGT GACCTCAAGC AGCCAGCCCG
641 TCACCTGCAA CGTGGCCCAC CCAGCCACCA ACACCAAAGT
681 GGACAAGACC GTTGCGCCCT CGACATGCAG CAAGCCCACG
721 TGCCCACCCC CTGAACTCCT GGGGGGACCG TCTGTCTTCA
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 761 TCTTCCCCCC AAAACCCAAG GACACCCTCA TGATCTCACG
 801 CACCCCCGAG GTCACATGCG TGGTGGTGGA CGTGAGCCAG
 841 GATGACCCCG AGGTGCAGTT CACATGGTAC ATAAACAACG
 881 AGCAGGTGCG CACCGCCCGG CCGCCGCTAC GGGAGCAGCA
 921 GTTCAACAGC ACGATCCGCG TGGTCAGCAC CCTCCCCATC
 961 GCGCACCAGG ACTGGCTGAG GGGCAAGGAG TTCAAGTGCA
1001 AAGTCCACAA CAAGGCACTC CCGGCCCCCA TCGAGAAAAC
1041 CATCTCCAAA GCCAGAGGGC AGCCCCTGGA GCCGAAGGTC
1081 TACACCATGG GCCCTCCCCG GGAGGAGCTG AGCAGCAGGT
1121 CGGTCAGCCT GACCTGCATG ATCAACGGCT TCTACCCTTC
1162 CGACATCTCG GTGGAGTGGG AGAAGAACGG GAAGGCAGAG
1201 GACAACTACA AGACCACGCC GGCCGTGCTG GACAGCGACG
1241 GCTCCTACTT CCTCTACAAC AAGCTCTCAG TGCCCACGAG
1281 TGAGTGGCAG CGGGGCGACG TCTTCACCTG CTCCGTGATG
1321 CACGAGGCCT TGCACAACCA CTACACGCAG AAGTCCATCT
1361 CCCGCTCTCC GGGTAAA
```

Anti-sense Nucleic Acids

Anti-sense nucleic acids can be used to inhibit the function of CD83. In general, the function of CD83 RNA is inhibited, for example, by administering to a mammal a nucleic acid that can inhibit the functioning of CD83 RNA. Nucleic acids that can inhibit the function of a CD83RNA can be generated from coding and non-coding regions of the CD83 gene. However, nucleic acids that can inhibit the function of a CD83 RNA are often selected to be complementary to CD83 nucleic acids that are naturally expressed in the mammalian cell to be treated with the methods of the invention. In some embodiments, the nucleic acids that can inhibit CD83 RNA functions are complementary to CD83 sequences found near the 5' end of the CD83 coding region. For example, nucleic acids that can inhibit the function of a CD83 RNA can be complementary to the 5' region of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10.

A nucleic acid that can inhibit the functioning of a CD83 RNA need not be 100% complementary to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Instead, some variability the sequence of the nucleic acid that can inhibit the functioning of a CD83 RNA is permitted. For example, a nucleic acid that can inhibit the functioning of a CD83 RNA from a human can be complementary to a nucleic acid encoding either a human or a mouse CD83 gene product.

Moreover, nucleic acids that can hybridize under moderately or highly stringent hybridization conditions to a nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10 are sufficiently complementary to inhibit the functioning of a CD83 RNA and can be utilized in the methods of the invention.

"Stringent hybridization conditions" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization are somewhat sequence dependent, and may differ depending upon the environmental conditions of the nucleic acid. For example, longer sequences tend to hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Laboratory Techniques in Biochemistry and Molecular biology-Hybridization with Nucleic Acid Probes, page 1, chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays" Elsevier, New York (1993). See also, J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, N.Y., pp 9.31-9.58 (1989); J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, N.Y. (3rd ed. 2001).

Generally, highly stringent hybridization and wash conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific double-stranded sequence at a defined ionic strength and pH. For example, under "highly stringent conditions" or "highly stringent hybridization conditions" a nucleic acid will hybridize to its complement to a detectably greater degree than to other sequences (e.g., at least 2- fold over background). By controlling the stringency of the hybridization and/or washing conditions nucleic acids that are 100% complementary can be hybridized.
For DNA-DNA hybrids, the T_m can be approximated from the equation of Meinkoth and Wahl Anal. Biochem. 138:267-284 (1984):

$$T_m\ 81.5°C + 16.6 (\log M) +0.41 (\%GC) - 0.61 (\% \text{form}) - 500/L$$

where M is the molarity of monovalent cations, %GC is the percentage of guanosine and cytosine nucleotides in the DNA, % form is the percentage of formamide in the hybridization solution, and L is the length of the hybrid in base pairs. The T_m is the temperature (under defined ionic strength and pH) at which

50% of a complementary target sequence hybridizes to a perfectly matched probe.

Very stringent conditions are selected to be equal to the T_m for a particular probe.

Alternatively, stringency conditions can be adjusted to allow some mismatching in sequences so that lower degrees of similarity can hybridize. Typically, stringent conditions will be those in which the salt concentration is less than about 1.5 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (e.g., 10 to 50 nucleotides) and at least about 60°C for long probes (e.g., greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide.

Exemplary low stringency conditions include hybridization with a buffer solution of 30 to 35% formamide, 1 M NaCl, 1% SDS (sodium dodecyl sulphate) at 37°C, and a wash in 1X to 2X SSC (20X SSC = 3.0 M NaCl and 0.3 M trisodium citrate) at 50 to 55°C. Exemplary moderate stringency conditions include hybridization in 40 to 45% formamide, 1.0 M NaCl, 1% SDS at 37°C, and a wash in 0.5X to 1X SSC at 55 to 60°C. Exemplary high stringency conditions include hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0. 1X SSC at 60 to 65°C.

The degree of complementarity or sequence identity of hybrids obtained during hybridization is typically a function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. The type and length of hybridizing nucleic acids also affects whether hybridization will occur and whether any hybrids formed will be stable under a given set of hybridization and wash conditions.

An example of stringent hybridization conditions for hybridization of complementary nucleic acids that have more than 100 complementary residues on a filter in a Southern or Northern blot is 50% formamide with 1 mg of heparin at 42°C, with the hybridization being carried out overnight. An example of highly stringent conditions is 0.1 5 M NaCl at 72°C for about 15 minutes. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (see also, Sambrook, infra). Often, a high stringency wash is preceded by a low

stringency wash to remove background probe signal. An example of medium stringency for a duplex of, e.g., more than 100 nucleotides, is 1x SSC at 45°C for 15 minutes. An example low stringency wash for a duplex of, e.g., more than 100 nucleotides, is 4-6x SSC at 40°C for 15 minutes. For short probes (e.g., about 10 to 50 nucleotides), stringent conditions typically involve salt concentrations of less than about 1.0M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3, and the temperature is typically at least about 30°C.

Stringent conditions can also be achieved with the addition of destabilizing agents such as formamide. In general, a signal to noise ratio of 2x (or higher) than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization. Nucleic acids that do not hybridize to each other under stringent conditions are still substantially identical if the proteins that they encode are substantially identical. This occurs, e.g., when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code.

The following are examples of sets of hybridization/wash conditions that may be used to detect and isolate homologous nucleic acids that are substantially identical to reference nucleic acids of the present invention: a reference nucleotide sequence preferably hybridizes to the reference nucleotide sequence in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 2X SSC, 0.1% SDS at 50°C, more desirably in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 1X SSC, 0.1% SDS at 50°C, more desirably still in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 0.5X SSC, 0.1% SDS at 50°C, preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 50°C, more preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 65°C.

In general, T_m is reduced by about 1°C for each 1% of mismatching. Thus, T_m, hybridization, and/or wash conditions can be adjusted to hybridize to sequences of the desired sequence identity. For example, if sequences with >90% identity are sought, the T_m can be decreased 10°C. Generally, stringent

conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific sequence and its complement at a defined ionic strength and pH. However, severely stringent conditions can utilize a hybridization and/or wash at 1, 2, 3, or 4°C lower than the thermal melting point (T_m); moderately stringent conditions can utilize a hybridization and/or wash at 6, 7, 8, 9, or 10°C lower than the thermal melting point (T_m); low stringency conditions can utilize a hybridization and/or wash at 11, 12, 13, 14, 15, or 20°C lower than the thermal melting point (T_m).

If the desired degree of mismatching results in a T_m of less than 45°C (aqueous solution) or 32°C (formamide solution), it is preferred to increase the SSC concentration so that a higher temperature can be used. An extensive guide to the hybridization of nucleic acids is found in Tijssen (1993) Laboratory Techniques in Biochemistry and Molecular Biology-Hybridization with Nucleic Acid Probes, Part 1, Chapter 2 (Elsevier, New York); and Ausubel et al., eds. (1995) Current Protocols in Molecular Biology, Chapter 2 (Greene Publishing and Wiley - Interscience, New York). See Sambrook et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Plainview, New York). Using these references and the teachings herein on the relationship between T_m, mismatch, and hybridization and wash conditions, those of ordinary skill can generate variants of the present homocysteine S-methyltransferase nucleic acids.

Precise complementarity is therefore not required for successful duplex formation between a nucleic acid that can inhibit a CD83 RNA and the complementary coding sequence of a CD83 RNA. Inhibitory nucleic acid molecules that comprise, for example, 2, 3, 4, or 5 or more stretches of contiguous nucleotides that are precisely complementary to a CD83 coding sequence, each separated by a stretch of contiguous nucleotides that are not complementary to adjacent CD83 coding sequences, can inhibit the function of CD83 RNA. In general, each stretch of contiguous nucleotides is at least 4, 5, 6, 7, or 8 or more nucleotides in length. Non-complementary intervening sequences are preferably 1, 2, 3, or 4 nucleotides in length. One skilled in the art can easily use the calculated melting point of an anti-sense nucleic acid hybridized to a sense nucleic acid to determine the degree of mismatching that

will be tolerated between a particular anti-sense nucleic acid and a particular CD83 RNA.

Nucleic acids that complementary a CD83 RNA can be administered to a mammal or to directly to the site of the inappropriate immune system activity. Alternatively, nucleic acids that are complementary to a CD83 RNA can generated by transcription from an expression cassette that has been administered to a mammal. For example, a complementary RNA can be transcribed from a CD83 nucleic acid that has been inserted into an expression cassette in the 3' to 5' orientation, that is, opposite to the usual orientation employed to generate sense RNA transcripts. Hence, to generate a complementary RNA that can inhibit the function of an endogenous CD83 RNA, the promoter would be positioned to transcribe from a 3' site towards the 5' end of the CD83 coding region.

In some embodiments an RNA that can inhibit the function of an endogenous CD83 RNA is an anti-sense oligonucleotide. The anti-sense oligonucleotide is complementary to at least a portion of the coding sequence of a gene comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Such anti-sense oligonucleotides are generally at least six nucleotides in length, but can be about 8, 12, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides long. Longer oligonucleotides can also be used. CD83 anti-sense oligonucleotides can be provided in a DNA construct and introduced into cells whose division is to be decreased, for example, into CD4+ T cells, Th-1 cells, Th-2 cells or lymphocyte precursor cells.

Anti-sense oligonucleotides can be composed of deoxyribonucleotides, ribonucleotides, or a combination of both. Oligonucleotides can be synthesized endogenously from transgenic expression cassettes or vectors as described herein. Alternatively, such oligonucleotides can be synthesized manually or by an automated synthesizer, by covalently linking the 5' end of one nucleotide with the 3' end of another nucleotide with non-phosphodiester internucleotide linkages such alkylphosphonates, phosphorothioates, phosphorodithioates, alkylphosphonothioates, alkylphosphonates, phosphoramidates, phosphate esters, carbamates, acetamidate, carboxymethyl esters, carbonates, and phosphate

triesters. See Brown, 1994, Meth. Mol. Biol. 20:1-8; Sonveaux, 1994, Meth. Mol. Biol. 26:1-72; Uhlmann et al., 1990, Chem. Rev. 90:543-583.

CD83 anti-sense oligonucleotides can be modified without affecting their ability to hybridize to a CD83 RNA. These modifications can be internal or at one or both ends of the anti-sense molecule. For example, internucleoside phosphate linkages can be modified by adding peptidyl, cholesteryl or diamine moieties with varying numbers of carbon residues between these moities and the terminal ribose. Modified bases and/or sugars, such as arabinose instead of ribose, or a 3', 5'-substituted oligonucleotide in which the 3' hydroxyl group or the 5' phosphate group are substituted, can also be employed in a modified anti-sense oligonucleotide. These modified oligonucleotides can be prepared by methods available in the art. Agrawal et al., 1992, Trends Biotechnol. 10:152-158; Uhlmann et al., 1990, Chem. Rev. 90:543-584; Uhlmann et al., 1987, Tetrahedron. Lett. 215:3539-3542.

In one embodiment of the invention, expression of a CD83 gene is decreased using a ribozyme. A ribozyme is an RNA molecule with catalytic activity. See, e.g., Cech, 1987, Science 236: 1532-1539; Cech, 1990, Ann. Rev. Biochem. 59:543-568; Cech, 1992, Curr. Opin. Struct. Biol. 2: 605-609; Couture and Stinchcomb, 1996, Trends Genet. 12: 510-515. Ribozymes can be used to inhibit gene function by cleaving an RNA sequence, as is known in the art (see, e.g., Haseloff et al., U.S. Pat. No. 5,641,673).

CD83 nucleic acids complementary to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10 can be used to generate ribozymes that will specifically bind to mRNA transcribed from a CD83 gene. Methods of designing and constructing ribozymes that can cleave other RNA molecules in trans in a highly sequence specific manner have been developed and described in the art (see Haseloff et al. (1988), Nature 334:585-591). For example, the cleavage activity of ribozymes can be targeted to specific RNAs by engineering a discrete "hybridization" region into the ribozyme. The hybridization region contains a sequence complementary to the target RNA and thus specifically hybridizes with the target (see, for example, Gerlach et al., EP 321,201). The target sequence can be a segment of about 10, 12, 15, 20, or 50 contiguous nucleotides selected from a nucleotide sequence shown in SEQ ID NO:1, SEQ

ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Longer complementary sequences can be used to increase the affinity of the hybridization sequence for the target. The hybridizing and cleavage regions of the ribozyme can be integrally related; thus, upon hybridizing to the target RNA through the complementary regions, the catalytic region of the ribozyme can cleave the target.

Other CD83 Modulating Molecules

A wide variety of molecules may be used to modulate CD83 activity or function. Such molecules can also be used to modulate the immune system independent of CD83. Compositions and methods for modulating CD83 activity or expression can include these molecules as well as other components. Representative examples that are discussed in more detail below include transciption factors, RNA-binding factors, organic molecules, or peptides.

RNA-Binding Factors:

One class of molecules that can be used to modulate cytokine levels or GM-CSF levels by way of the CD83 gene is the RNA binding factors. Such factors include those described in PCT/EP01/14820 and other sources.

For example, the HuR protein (Genbank accession number U38175) has the ability to specifically bind to CD83 RNA at AU-rich elements or sites. Such AU-rich elements comprise sequences such as AUUUA (SEQ ID NO:49), AUUUUA (SEQ ID NO:50) and AUUUUUA (SEQ ID NO:51). Binding by such HuR proteins to CD83 mRNA is thought to increase the stability, transport and translation of CD83 mRNA, and thereby increase the expression of CD83 polypeptides. Hence, CD83 expression may be increase by administering HuR proteins or nucleic acids to a mammal.

Conversely, CD83 expression may be decreased by administering factors that block HuR binding to CD83 mRNA. Factors that block HuR binding include proteins or nucleic acids that can bind to the AU-rich elements normally bound by HuR, for example, nucleic acids or anti-sense nucleic acids that are complementary to AU-rich elements.

Organic Molecules:

Numerous organic molecules may be used to modulate the immune system. These compounds include any compound that can interact with a component of the immune system. Such compounds may interact directly with CD83, indirectly with CD83 or with some other polypeptide, cell or factor that plays a role in the function of the immune system. In some embodiments, the organic molecule can bind to a CD83 polypeptide or a CD83 nucleic acid.

Organic molecules can be tested or assayed for their ability to modulate CD83 activity, CD83 function or for their ability to modulate components of the immune system. For example, within one embodiment of the invention suitable organic molecules may be selected either from a chemical library, wherein chemicals are assayed individually, or from combinatorial chemical libraries where multiple compounds are assayed at once, then deconvoluted to determine and isolate the most active compounds.

Representative examples of such combinatorial chemical libraries include those described by Agrafiotis et al., "System and method of automatically generating chemical compounds with desired properties," U.S. Patent No. 5,463,564; Armstrong, R.W., "Synthesis of combinatorial arrays of organic compounds through the use of multiple component combinatorial array syntheses," WO 95/02566; Baldwin, J.J. et al., "Sulfonamide derivatives and their use," WO 95/24186; Baldwin, J.J. et al., "Combinatorial dihydrobenzopyran library," WO 95/30642; Brenner, S., "New kit for preparing combinatorial libraries," WO 95/16918; Chenera, B. et al., "Preparation of library of resin-bound aromatic carbocyclic compounds," WO 95/16712; Ellman, J.A., "Solid phase and combinatorial synthesis of benzodiazepine compounds on a solid support," U.S. Patent No. 5,288,514; Felder, E. et al., "Novel combinatorial compound libraries," WO 95/16209; Lerner, R. et al., "Encoded combinatorial chemical libraries," WO 93/20242; Pavia, M.R. et al., "A method for preparing and selecting pharmaceutically useful non-peptide compounds from a structurally diverse universal library," WO 95/04277; Summerton, J.E. and D.D. Weller, "Morpholino-subunit combinatorial library and method," U.S. Patent No. 5,506,337; Holmes, C., "Methods for the Solid Phase Synthesis of Thiazolidinones, Metathiazanones, and Derivatives thereof," WO 96/00148; Phillips, G.B. and G.P. Wei, "Solid-phase

Synthesis of Benzimidazoles," *Tet. Letters 37*:4887-90, 1996; Ruhland, B. et al., "Solid-supported Combinatorial Synthesis of Structurally Diverse □□-Lactams," *J. Amer. Chem. Soc. 111*:253-4, 1996; Look, G.C. et al., "The Indentification of Cyclooxygenase-1 Inhibitors from 4-Thiazolidinone Combinatorial Libraries," *Bioorg and Med. Chem. Letters 6*:707-12, 1996.

Peptides:

Peptide molecules that modulate the immune system may be obtained through the screening of combinatorial peptide libraries. Such libraries may either be prepared by one of skill in the art (*see e.g.*, U.S. Patent Nos. 4,528,266 and 4,359,535, and Patent Cooperation Treaty Publication Nos. WO 92/15679, WO 92/15677, WO 90/07862, WO 90/02809, or purchased from commercially available sources (*e.g.*, New England Biolabs Ph.D.™ Phage Display Peptide Library Kit).

Methods of Using the CD83 Mutant Mouse

In one embodiment, the invention provides a method for identifying ligands, receptors, therapeutic drugs and other molecules that can modulate the phenotype of the mutant CD83 in vivo. This method involves administering a test compound to the mutant CD83 mouse of the invention and observing whether the compound causes a change in the phenotype of the mutant mouse. Changes in phenotype that are of interest include increases or decreases in T cells (especially CD4+ T cells), increases or decreases in GMCSF, IL-2, IL-4 or IL-10 cytokine production, increases or decreases in inflammation, increases or decreases in dendritic cell function and other T cell responses known to one of skill in the art.

Test compounds can be screened in vitro to ascertain whether they interact directly with CD83. In vitro screening can, for example, identify whether a test compound or molecule can bind to the cytoplasmic tail or the membrane-associated portions of CD83. Such information, combined with observation of the in vivo phenotype before and after administration of the test compound provides further insight into the function of CD83 and provides

targets for manipulation T cell activation and other functions modulated by CD83.

The invention is not limited to identification of molecules that directly associate with CD83. The in vivo screening methods provided herein can, also identify test compounds that have an indirect effect on CD83, or that partially or completely replace a function of CD83.

Increases or decreases in T cell numbers can be observed in blood samples or in samples obtained from thymus, spleen or lymph node tissues. In order to observe the activation of T cells and/or the interaction of T cells and dendritic cells, dendritic cells can be pulsed with antigens ex vivo and then injected into mice to prime CD4+ T cells in draining lymphoid organs. *See* Inaba et al., J. Exp. Med. 172: 631-640, 1990; Liu, et al., J. Exp. Med. 177: 1299-1307, 1993; Sornasse et al., J. Exp. Med. 175: 15-21, 1992. Antigens can also be deposited intramuscularly and dendritic cells from the corresponding afferent lymphatics can carry that antigen in a form stimulatory for T cells. Bujdoso et al., J. Exp. Med. 170: 1285-1302, 1989. According to the invention, factors stimulating the interaction of dendritic cells with T cells in vivo can be identified by administering antigens in this manner and then observing how T cell respond, e.g. by observing whether T cell activation occurs.

Increases or decreases in cytokine levels can be observed by methods provided herein or by other methods available in the art.

Compositions

The CD83 polypeptides and antibodies of the invention, including their salts, are administered so as to achieve a reduction in at least one symptom associated with an infection, indication or disease.

To achieve the desired effect(s), the polypeptide or antibody, a variant thereof or a combination thereof, may be administered as single or divided dosages, for example, of at least about 0.01 mg/kg to about 500 to 750 mg/kg, of at least about 0.01 mg/kg to about 300 to 500 mg/kg, at least about 0.1 mg/kg to about 100 to 300 mg/kg or at least about 1 mg/kg to about 50 to 100 mg/kg of body weight, although other dosages may provide beneficial results. The amount administered will vary depending on various factors including, but not limited to,

the polypeptide or antibody chosen, the disease, the weight, the physical condition, the health, the age of the mammal, whether prevention or treatment is to be achieved, and if the polypeptide or antibody is chemically modified. Such factors can be readily determined by the clinician employing animal models or other test systems that are available in the art.

Administration of the therapeutic agents in accordance with the present invention may be in a single dose, in multiple doses, in a continuous or intermittent manner, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of the CD83 polypeptides and antibodies of the invention may be essentially continuous over a preselected period of time or may be in a series of spaced doses. Both local and systemic administration is contemplated.

To prepare the composition, CD83 polypeptides and antibodies are synthesized or otherwise obtained, purified as necessary or desired and then lyophilized and stabilized. The polypeptide or antibody can then be adjusted to the appropriate concentration, and optionally combined with other agents. The absolute weight of a given polypeptide or antibody included in a unit dose can vary widely. For example, about 0.01 to about 2 g, or about 0.1 to about 500 mg, of at least one polypeptide or antibody of the invention, or a plurality of CD83 polypeptides and antibodies specific for a particular cell type can be administered. Alternatively, the unit dosage can vary from about 0.01 g to about 50 g, from about 0.01 g to about 35 g, from about 0.1 g to about 25 g, from about 0.5 g to about 12 g, from about 0.5 g to about 8 g, from about 0.5 g to about 4 g, or from about 0.5 g to about 2 g.

Daily doses of the CD83 polypeptides or antibodies of the invention can vary as well. Such daily doses can range, for example, from about 0.1 g/day to about 50 g/day, from about 0.1 g/day to about 25 g/day, from about 0.1 g/day to about 12 g/day, from about 0.5 g/day to about 8 g/day, from about 0.5 g/day to about 4 g/day, and from about 0.5 g/day to about 2 g/day.

Thus, one or more suitable unit dosage forms comprising the therapeutic CD83 polypeptides or antibodies of the invention can be administered by a variety of routes including oral, parenteral (including subcutaneous, intravenous,

intramuscular and intraperitoneal), rectal, dermal, transdermal, intrathoracic, intrapulmonary and intranasal (respiratory) routes. The therapeutic CD83 polypeptides or antibodies may also be formulated for sustained release (for example, using microencapsulation, see WO 94/ 07529, and U.S. Patent No.4,962,091). The formulations may, where appropriate, be conveniently presented in discrete unit dosage forms and may be prepared by any of the methods well known to the pharmaceutical arts. Such methods may include the step of mixing the therapeutic agent with liquid carriers, solid matrices, semi-solid carriers, finely divided solid carriers or combinations thereof, and then, if necessary, introducing or shaping the product into the desired delivery system.

When the therapeutic CD83 polypeptides or antibodies of the invention are prepared for oral administration, they are generally combined with a pharmaceutically acceptable carrier, diluent or excipient to form a pharmaceutical formulation, or unit dosage form. For oral administration, the CD83 polypeptides or antibodies may be present as a powder, a granular formulation, a solution, a suspension, an emulsion or in a natural or synthetic polymer or resin for ingestion of the active ingredients from a chewing gum. The active CD83 polypeptides or antibodies may also be presented as a bolus, electuary or paste. Orally administered therapeutic CD83 polypeptides or antibodies of the invention can also be formulated for sustained release, e.g., the CD83 polypeptides or antibodies can be coated, micro-encapsulated, or otherwise placed within a sustained delivery device. The total active ingredients in such formulations comprise from 0.1 to 99.9% by weight of the formulation.

By "pharmaceutically acceptable" it is meant a carrier, diluent, excipient, and/or salt that is compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Pharmaceutical formulations containing the therapeutic CD83 polypeptides or antibodies of the invention can be prepared by procedures known in the art using well-known and readily available ingredients. For example, the polypeptide or antibody can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, solutions, suspensions, powders, aerosols and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include buffers, as well as fillers and extenders

such as starch, cellulose, sugars, mannitol, and silicic derivatives. Binding agents can also be included such as carboxymethyl cellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone. Moisturizing agents can be included such as glycerol, disintegrating agents such as calcium carbonate and sodium bicarbonate. Agents for retarding dissolution can also be included such as paraffin. Resorption accelerators such as quaternary ammonium compounds can also be included. Surface active agents such as cetyl alcohol and glycerol monostearate can be included. Adsorptive carriers such as kaolin and bentonite can be added. Lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols can also be included. Preservatives may also be added. The compositions of the invention can also contain thickening agents such as cellulose and/or cellulose derivatives. They may also contain gums such as xanthan, guar or carbo gum or gum arabic, or alternatively polyethylene glycols, bentones and montmorillonites, and the like.

For example, tablets or caplets containing the CD83 polypeptides or antibodies of the invention can include buffering agents such as calcium carbonate, magnesium oxide and magnesium carbonate. Caplets and tablets can also include inactive ingredients such as cellulose, pregelatinized starch, silicon dioxide, hydroxy propyl methyl cellulose, magnesium stearate, microcrystalline cellulose, starch, talc, titanium dioxide, benzoic acid, citric acid, corn starch, mineral oil, polypropylene glycol, sodium phosphate, zinc stearate, and the like. Hard or soft gelatin capsules containing at least one polypeptide or antibody of the invention can contain inactive ingredients such as gelatin, microcrystalline cellulose, sodium lauryl sulfate, starch, talc, and titanium dioxide, and the like, as well as liquid vehicles such as polyethylene glycols (PEGs) and vegetable oil. Moreover, enteric-coated caplets or tablets containing one or more CD83 polypeptides or antibodies of the invention are designed to resist disintegration in the stomach and dissolve in the more neutral to alkaline environment of the duodenum.

The therapeutic CD83 polypeptides or antibodies of the invention can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular,

subcutaneous, intraperitoneal or intravenous routes. The pharmaceutical formulations of the therapeutic CD83 polypeptides or antibodies of the invention can also take the form of an aqueous or anhydrous solution or dispersion, or alternatively the form of an emulsion or suspension or salve.

Thus, the therapeutic CD83 polypeptides or antibodies may be formulated for parenteral administration (e.g., by injection, for example, bolus injection or continuous infusion) and may be presented in unit dose form in ampules, pre-filled syringes, small volume infusion containers or in multi-dose containers. As noted above, preservatives can be added to help maintain the shelve life of the dosage form. The active CD83 polypeptides or antibodies and other ingredients may form suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active CD83 polypeptides or antibodies and other ingredients may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

These formulations can contain pharmaceutically acceptable carriers, vehicles and adjuvants that are well known in the art. It is possible, for example, to prepare solutions using one or more organic solvent(s) that is/are acceptable from the physiological standpoint, chosen, in addition to water, from solvents such as acetone, ethanol, isopropyl alcohol, glycol ethers such as the products sold under the name "Dowanol," polyglycols and polyethylene glycols, C_1-C_4 alkyl esters of short-chain acids, ethyl or isopropyl lactate, fatty acid triglycerides such as the products marketed under the name "Miglyol," isopropyl myristate, animal, mineral and vegetable oils and polysiloxanes.

It is possible to add, if necessary, an adjuvant chosen from antioxidants, surfactants, other preservatives, film-forming, keratolytic or comedolytic agents, perfumes, flavorings and colorings. Antioxidants such as t-butylhydroquinone, butylated hydroxyanisole, butylated hydroxytoluene and α-tocopherol and its derivatives can be added.

Also contemplated are combination products that include one or more CD83 polypeptides or antibodies of the present invention and one or more other anti-microbial agents. For example, a variety of antibiotics can be included in the

pharmaceutical compositions of the invention, such as aminoglycosides (e.g., streptomycin, gentamicin, sisomicin, tobramycin and amicacin), ansamycins (e.g. rifamycin), antimycotics (e.g. polyenes and benzofuran derivatives), β-lactams (e.g. penicillins and cephalosporins), chloramphenical (including thiamphenol and azidamphenicol), linosamides (lincomycin, clindamycin), macrolides (erythromycin, oleandomycin, spiramycin), polymyxins, bacitracins, tyrothycin, capreomycin, vancomycin, tetracyclines (including oxytetracycline, minocycline, doxycycline), phosphomycin and fusidic acid.

Additionally, the CD83 polypeptides or antibodies are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active polypeptide or antibody, for example, in a particular part of the intestinal or respiratory tract, possibly over a period of time. Coatings, envelopes, and protective matrices may be made, for example, from polymeric substances, such as polylactide-glycolates, liposomes, microemulsions, microparticles, nanoparticles, or waxes. These coatings, envelopes, and protective matrices are useful to coat indwelling devices, e.g., stents, catheters, peritoneal dialysis tubing, draining devices and the like.

For topical administration, the therapeutic agents may be formulated as is known in the art for direct application to a target area. Forms chiefly conditioned for topical application take the form, for example, of creams, milks, gels, dispersion or microemulsions, lotions thickened to a greater or lesser extent, impregnated pads, ointments or sticks, aerosol formulations (e.g., sprays or foams), soaps, detergents, lotions or cakes of soap. Other conventional forms for this purpose include wound dressings, coated bandages or other polymer coverings, ointments, creams, lotions, pastes, jellies, sprays, and aerosols. Thus, the therapeutic CD83 polypeptides or antibodies of the invention can be delivered via patches or bandages for dermal administration. Alternatively, the polypeptide or antibody can be formulated to be part of an adhesive polymer, such as polyacrylate or acrylate/vinyl acetate copolymer. For long-term applications it might be desirable to use microporous and/or breathable backing laminates, so hydration or maceration of the skin can be minimized. The backing layer can be any appropriate thickness that will provide the desired

protective and support functions. A suitable thickness will generally be from about 10 to about 200 microns.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active CD83 polypeptides or antibodies can also be delivered via iontophoresis, e.g., as disclosed in U.S. Patent Nos. 4,140,122; 4,383,529; or 4,051,842. The percent by weight of a therapeutic agent of the invention present in a topical formulation will depend on various factors, but generally will be from 0.01% to 95% of the total weight of the formulation, and typically 0.1-85% by weight.

Drops, such as eye drops or nose drops, may be formulated with one or more of the therapeutic CD83 polypeptides or antibodies in an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs. Drops can be delivered via a simple eye dropper-capped bottle, or via a plastic bottle adapted to deliver liquid contents dropwise, via a specially shaped closure.

The therapeutic polypeptide or antibody may further be formulated for topical administration in the mouth or throat. For example, the active ingredients may be formulated as a lozenge further comprising a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the composition in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the composition of the present invention in a suitable liquid carrier.

The pharmaceutical formulations of the present invention may include, as optional ingredients, pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, and salts of the type that are available in the art. Examples of such substances include normal saline solutions such as physiologically buffered saline solutions and water. Specific non-limiting examples of the carriers and/or diluents that are useful in the pharmaceutical formulations of the present invention include water and physiologically

acceptable buffered saline solutions such as phosphate buffered saline solutions pH 7.0-8.0.

The CD83 polypeptides or antibodies of the invention can also be administered to the respiratory tract. Thus, the present invention also provides aerosol pharmaceutical formulations and dosage forms for use in the methods of the invention. In general, such dosage forms comprise an amount of at least one of the agents of the invention effective to treat or prevent the clinical symptoms of a specific infection, indication or disease. Any statistically significant attenuation of one or more symptoms of an infection, indication or disease that has been treated pursuant to the method of the present invention is considered to be a treatment of such infection, indication or disease within the scope of the invention.

Alternatively, for administration by inhalation or insufflation, the composition may take the form of a dry powder, for example, a powder mix of the therapeutic agent and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges, or, e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator, insufflator, or a metered-dose inhaler (see, for example, the pressurized metered dose inhaler (MDI) and the dry powder inhaler disclosed in Newinan, S. P. in Aerosols and the Lung, Clarke, S. W. and Davia, D. eds., pp. 197-224, Butterworths, London, England, 1984).

Therapeutic CD83 polypeptides or antibodies of the present invention can also be administered in an aqueous solution when administered in an aerosol or inhaled form. Thus, other aerosol pharmaceutical formulations may comprise, for example, a physiologically acceptable buffered saline solution containing between about 0.1 mg/ml and about 100 mg/ml of one or more of the CD83 polypeptides or antibodies of the present invention specific for the indication or disease to be treated. Dry aerosol in the form of finely divided solid polypeptide or antibody or nucleic acid particles that are not dissolved or suspended in a liquid are also useful in the practice of the present invention. CD83 polypeptides or antibodies of the present invention may be formulated as dusting powders and comprise finely divided particles having an average particle size of between about 1 and 5 μm, alternatively between 2 and 3 μm. Finely divided particles

may be prepared by pulverization and screen filtration using techniques well known in the art. The particles may be administered by inhaling a predetermined quantity of the finely divided material, which can be in the form of a powder. It will be appreciated that the unit content of active ingredient or ingredients contained in an individual aerosol dose of each dosage form need not in itself constitute an effective amount for treating the particular infection, indication or disease since the necessary effective amount can be reached by administration of a plurality of dosage units. Moreover, the effective amount may be achieved using less than the dose in the dosage form, either individually, or in a series of administrations.

For administration to the upper (nasal) or lower respiratory tract by inhalation, the therapeutic CD83 polypeptides or antibodies of the invention are conveniently delivered from a nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Nebulizers include, but are not limited to, those described in U.S. Patent Nos. 4,624,251; 3,703,173; 3,561 ,444; and 4,635,627. Aerosol delivery systems of the type disclosed herein are available from numerous commercial sources including Fisons Corporation (Bedford, Mass.), Schering Corp. (Kenilworth, NJ) and American Pharmoseal Co., (Valencia, CA). For intra-nasal administration, the therapeutic agent may also be administered via nose drops, a liquid spray, such as via a plastic bottle atomizer or metered-dose inhaler. Typical of atomizers are the Mistometer (Wintrop) and the Medihaler (Riker).

Furthermore, the active ingredients may also be used in combination with other therapeutic agents, for example, pain relievers, anti-inflammatory agents, antihistamines, bronchodilators and the like, whether for the conditions described or some other condition.

The present invention further pertains to a packaged pharmaceutical composition for controlling microbial infections such as a kit or other container. The kit or container holds a therapeutically effective amount of a pharmaceutical

composition for controlling microbial infections and instructions for using the pharmaceutical composition for control of the microbial infection. The pharmaceutical composition includes at least one polypeptide or antibody of the present invention, in a therapeutically effective amount such that the selected disease or immunological condition is controlled.

The invention will be further described by reference to the following detailed examples, which are given for illustration of the invention, and are not intended to be limiting thereof.

EXAMPLE 1: Mouse Mutation and Characterization

Mutant Generation

Male C57BL6 mice received 3 weekly injections of N-ethyl-N-nitrosourea (ENU) at a concentration of 100mg/kg. N-Ethyl-N-nitrosourea was quantified prior to injection by spectrophotometry. Mice that regained fertility after a minimum period of 12 weeks were then used to generate pedigree founder G1 animals. G1 male mice were crossed to C57BL6J females and their female progeny (G2 animals) crossed back to their fathers to generate G3 animals for screening.

G3 mice were weaned at 3 weeks of age. Each animal then underwent a series of screens designed to assess a number of parameters, including immune function, inflammatory response and bone development. In the initial screen, conducted at 6 weeks of age, 150-200ul of whole blood was collected by retro-orbital bleed into heparinized tubes. Cells were pelleted and red blood cells lysed. Samples were then stained with antibodies to cell surface markers expressed on distinct lymphoid and myeloid sub-populations. These samples were analyzed by flow-cytometry.

Mutant Identification

A group of 27 G3 mice from 2 different pedigrees, pedigree 9 and pedigree 57 (i.e. derived from 2 distinct G1 fathers) were analyzed in this screen. Two animals from pedigree 9 were identified as having a reduced (>2 standard deviation from normal) percentage of CD4+ T cells in peripheral blood (Figure 1). Both animals were descended from the same G1 and shared the same

mother. All other animals screened on that day had a normal percentage of CD4+ T cells. The number of phenodeviants identified (2 from a litter of 9 animals) was suggestive of a trait controlled by a single gene and inherited in a Mendelian fashion.

A second litter generated from Pedigree 9 bred to G2 daughter #4 exhibited an identical phenotype with reduced numbers of CD4+ T cells, further suggesting that the trait had a genetic basis. The phenotype was designated LCD4.1 (Low CD4 Mutant # 1) and was used for mapping experiments.

Mutation Mapping

In order to map the LCD4.1 mutant phenotype, affected G3 male mice (presumptive homozygous for the mutation) were bred to female animals from the C3HeB/FeJ strain to generate F1 progeny. These F1 females (presumptively heterozygous for the mutation) were then mated back to their affected father to generate N2 progeny.

Blood was collected from N2 animals and flow cytometric analysis was performed to identify CD4+ T cells. For a phenotype controlled by a single gene, breeding homozygous fathers to heterozygous daughters should yield 50% normal N2 animals and 50% affected N2 animals. This ratio of normal to affected animals was observed in the N2 generation: Multiple N2 animals exhibited a reduced percentage of CD4+ T cells, indicating that the phenotype was heritable (Figure 2).

DNA samples were prepared from samples of tail tissue collected from these N2 mice and used for a genome scan, using a collection of assembled markers, and performed on the ABI 3100 DNA analyzer. Initial genetic linkage was seen to the tip of chromosome 13, where the closest microsatellite marker was D13Mit139 with a LOD score of 8.2. By calculating upper and lower confidence limits, the mutant gene was located between 13.4 and 29.6 cM on chromosome 13. Through additional genotyping, this region was reduced to an 11 cM interval on chromosome 13. No significant linkage to other chromosomal regions was seen.

Mutation Identification

A candidate gene, CD83, was identified for gene-testing based upon its reported position within the interval. CD83 has previously been used as a marker of dendritic cell activation, suggesting that it might play a role in dendritic cell function and hence in regulating T cell development and function.

Sequence analysis of the mutant DNA revealed a mutation in the stop codon of CD83. All affected animals were homozygous for this mutation while non-affected animals carried one wild-type allele and one mutant allele (Figure 3 and Figure 4). The mutation destroyed the stop codon and resulted in the addition of a unique 55 amino acid tail to the C-terminus of CD83 (Figure 5).

Additional Functional Data

A reduction in CD4+ T cells was seen in peripheral blood, spleen tissues and lymph nodes from homozygous LCD4.1 mice. Although there was a reduced number of CD4+ T cells in the thymus there is no overt block in the developmental process and there was no alteration in B cell development in the bone marrow. Histological evaluation of thymus, spleen and lymph nodes from affected mice revealed no gross alteration in tissue architecture.

Dendritic cells can be differentiated from bone marrow of wild type mice by culture in GM-CSF. These cells can be characterized by the surface expression of dendritic cell markers, including CD86 and CD11c. Both LCD4.1 affected and normal animals were capable of giving rise to CD86+CD11c+ cells under these culture conditions. LCD4.1 mutant mice thus were capable of generating dendritic cells under in vitro culture conditions. These data suggest that the phenotype seen in LCD4.1 mice is not due to a failure of dendritic cells to develop but rather may reflect a defect in function.

To track dendritic cells the sensitizing agent FITC was applied to the dorsal surface of the ears of LCD4.1 affected and wild-type mice. FITC was picked up by dendritic cells that then migrated to the draining auricular lymph nodes, where the presence of the FITC label on the dendritic cell surface permitted detection by flow-cytometry. FITC labeled cells expressing CD86 were detected in equal proportions in draining lymph node from normal and affected LCD4.1 mice. These data indicate that LCD4.1 mutant animals are

capable of generating dendritic cells in vivo and that these cells are able to pick up antigen in the ear and travel to the draining lymph node.

EXAMPLE 2: CD83 and CD4+ T Cell Function

Materials and Methods

Spleens were removed from wild type and mutant mice and digested with collagenase to liberate dendritic cells. Spleens were stained for surface expression of CD4 (helper T cells) and CD11c (dendritic cells). Cells expressing these markers were purified by fluorescence activated cell sorting (FACS sorting). CD11c and CD4+ positive cells were also purified from an allogeneic mouse strain, BALBc.

Mixed lymphocyte cultures were set up using purified cell populations. Dendritic cells from BALBc animals were used to stimulate CD4+ T cells from wild type and mutant mice. In a reciprocal experiment dendritic cells prepared from wild type and mutant mice were used to stimulate BALBc CD4+ T cells. After 5 days in culture proliferative responses were measured by incorporation of tritiated thymidine.

Dendritic cells from wild type and mutant mice were both capable of activating allogeneic T cells, suggesting that dendritic cell function was unimpaired in the mutant animal (Figure 6a). In contrast CD4+ T cells from mutant animals exhibited a diminished response after 5 days of stimulation (Figure 6b).

These data suggest that the mutation in the CD83 gene has minimal effect on dendritic cells intrinsic function but rather has a profound effect upon T cell activity. The CD4+ T cell therefore may have a novel requirement for CD83 functionality on T cells during allogeneic activation. CD83 may be influencing the extent of CD4+ T cell activation or altering the duration of the CD4+ T cell proliferative response. The therapeutic manipulation of CD83 may thus represent a mechanism for the specific regulation of T cell function in the treatment of T cell mediated diseases, including autoimmune disorders. Antibodies capable of blocking CD83 function may be used as therapeutics in

the treatment of immune diseases whilst the activation of CD83 may have utility in enhancing immune responses in cancer and other circumstances.

Conclusion

Although CD83 has been described as a marker of dendritic cell activation there is little data as to its function in vivo. The mutation provided by the invention destabilizes or inactivates the protein and leads to impaired surface expression. As a consequence, CD4+ T cell function is impaired although the development of dendritic cells is not inhibited and mutant dendritic cells retain functionality. This results in the impaired development of CD4+ T cells. This impaired ability to activate T cells is also seen in a slight decrease in contact sensitivity responses in LCD4.1 mutant mice.

EXAMPLE 3: Mutant CD83 Have Different Cytokine Levels than Wild Type Mice

This Example demonstrates that $CD4^+$ T-cells from CD83 mutant animals express higher levels of IL-4 and lower levels of IL-2 compared to $CD4^+$ T-cells from CD83 wild type animals.

Methods for cell activation and cytokine measurements:

Spleens cells from 6-8-week-old homozygous CD83 wild type or CD83 mutant (LCD4.1) mice were used to isolate $CD4^+$ T-cells by positive selection using magnetic beads (Miltenyi Biotec). A 96 round bottom plate was coated with 50μL per well of a solution containing either 1 or 10 μg/mL of anti-CD3 and 0.1 or 0.2 μg/mL of anti-CD28 antibodies (both from Pharmingen) in PBS overnight. This plate was then washed using 150 μL of PBS three times. To this pre-coated plate, 20,000 $CD4^+$ T-cells (either wild type or CD83 mutant) were added in a 200 μL final volume of RPMI containing 10% FBS, 55 μM β-mercaptoethanol and antibiotics. The plates were then incubated in a CO_2 incubator at 37 °C for 44 to 72 hours. For determination of cytokine levels, supernatants were harvested and cytokines were measured using either a Cytometric Bead Array system (Pharmingen) or ELISA (R&D). For RNA

measurements, the cells were harvested and RNA was isolated using Tri reagent (Sigma). IL-10 and IL-4 mRNA levels were measured by reverse transcription and TaqMan (Applied Biosystems) analysis.

Results:

Figure 7 shows the IL-2, IL-4, IL-5, TNFα and IFNγ levels produced by either wild type or CD83 mutant CD4$^+$ T-cells. Purified cells were incubated as described above in the presence of 1 μg/mL of anti-CD3 and 0.2 μg/mL of anti-CD28 antibodies for 72 hours. The supernatants were then simultaneously analyzed for production of IL-2, IL-4, IL-5, TNFα and IFNγ using the cytometric bead array system from Pharmingen.

Figure 7 demonstrates that CD4$^+$ T-cells from CD83 mutant animals expressed higher levels of IL-4 and lower levels of IL-2 compared to CD4$^+$ T-cells from CD83 wild type animals. Other cytokines and a new set of stimulation assays were analyzed including the production levels of IL-10 and GMCSF by these cells (Figures 8 and 9). In both cases, cells from mutant animals produce larger amounts of IL-10 and GMCSF than did wild type animals. Figure 10 shows that mRNA levels for both IL-4 and IL-10 were increased in cells from activated mutant CD83, CD4$^+$ T-cells compared with cells from wild type animals.

EXAMPLE 4: Anti-CD83 Antibodies May Mimic the Effects of the CD83 Mutation

Methods for antibody testing:

For modulation of cytokine production by anti-CD83 antibodies, CD4$^+$ T-cells were isolated and activated as mentioned above in the presence of increasing concentrations of anti-CD83 antibodies. For proliferation assays, CD4$^+$ T-cells were isolated from an OT2tg [transgenic mice with a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide]. Dendritic cells were isolated from a C57BL6 mouse by a negative selection using B220 magnetic beads (Miltenyi Biotec) followed by positive selection using CD11-c magnetic beads (Milteny Biotec). Five thousand CD4$^+$ T-cells were then mixed

with five thousand dendritic cells in a 96 well plate in the presences of 1 μM OVA peptide using RPMI (55 μM BME, 10%FBS plus antibiotics) in a final 200uL volume. These cells were then incubated for 48 to 72 hours in a CO_2 incubator at 37°C and pulsed using [^{3}H] thymidine for 8 hours. Cells were then harvested and [^{3}H] thymidine incorporation was quantified using a top counter.

Results:

In some assays, anti-CD83 antibodies decreased production of IL-4 by activated $CD4^+$ T-cells in a dose dependent manner. Different antibody preparations did provide somewhat different degrees of inhibition of IL-4 production (Figure 11). Accordingly, the epitope and/or degree of affinity of the antibodies for the CD83 antigen may influence whether or not IL-4 production is significantly inhibited.

The effects of anti CD83 antibodies on proliferation of a peptide specific T-cell proliferation assay using the OT2 T-cell receptor (TCR) transgenic system were also observed. $CD4^+$ T-cells derived from these TCR transgenic animals express high levels of a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide and thus have high levels of proliferation when mixed with antigen presenting cells (dendritic cells were used) in the presence of the OVA peptide. In such assays, anti-CD83 antibodies were able to decrease proliferation of $CD4^+$ T-cells in this system (Figure 12). However, different antibody preparations had somewhat different effects on the proliferation of $CD4^+$ T-cells. Accordingly, the CD83 epitope and/or degree of affinity of the antibodies for the CD83 antigen may influence whether or not $CD4^+$ T-cell proliferation is significantly inhibited.

EXAMPLE 5: Increased T-Cell Proliferation by Transgenic Expression of CD83

This Example illustrates that over expression of CD83 in transgenic mice leads to increased T-cell proliferation.

Materials and Methods

A 34.3 kb fragment of normal mouse genomic DNA, including the ~18 kb coding region of the CD83 gene, as well as ~10.6 kb of upstream flanking sequences and ~5.7 kb of downstream sequences was microinjected into normal mouse one-cell embryos. Four individual founder animals were generated. Transgenic mice were then crossed to a male OT2tg mouse. Male offspring carrying both the CD83 and OT2 transgene were used to analyze peptide specific T-cell proliferation.

For proliferation assays, $CD4^+$ T-cells and dendritic cells were isolated from either OT2tg [transgenic mice with a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide] CD83 wild type or from OT2tg CD83 transgenic mice as described above (Example 4). Five thousand OT2tg $CD4^+$ T-cells from either wild type or CD83 transgenic animals were then mixed with five thousand wild type dendritic cells or five thousand CD83 transgenic dendritic cells in a 96 well plate in the presence of increasing concentrations of OVA peptide using RPMI (55 μM BME, 10%FBS plus antibiotics) in a final 200uL volume. These cells were then incubated for 48 to 72 hours in a CO_2 incubator at 37C and pulsed using [^{3}H] thymidine for 8 hours. Cells were then harvested and [^{3}H] thymidine incorporation was quantified using a top counter.

Results:

OT2tg $CD4^+$ T-cells derived from CD83 transgenic mice proliferated at higher rates than the same cell population derived from a CD83 wild type animal (Figure 13). This increased proliferation was seen at all the concentrations of OVA peptide tested. Whereas OT2tg $CD4^+$ T-cells derived from CD83 transgenic animals exhibited increased proliferation, dendritic cells from CD83 transgenic animals did not exhibit a substantial increase in proliferation. Therefore, it appears that transgenic expression in the $CD4^+$ T-cell, and not in dendritic cells is what led to the increased proliferation of $CD4^+$ T-cells.

EXAMPLE 6: Inhibition of proliferation of PHA activated human PBMCs by protein A purified rabbit anti mouse CD83 polyclonal sera.

This Example shows that antibodies raised against the mouse CD83 protein can inhibit proliferation of human peripheral blood mononuclear cells.

Materials and Methods

Rabbit polyclonal sera was raised against mouse CD83 protein by immunizing rabbits using a mouse CD83 external domain protein fused to a rabbit Ig domain (Figure 14). Pre-immune sera and anti-mouse polyclonal sera were then purified using a protein A column (Pharmacia Biotech) as described by the manufacturer, then dialyzed against PBS and stored at 4° C. To monitor the recognition of mouse CD83 protein by the polyclonal sera, which was obtained at different dates post immunization, a titer was obtained using an antigen specific ELISA (Figure 15). As illustrated by Figure 15, a good polyclonal response was obtained against the mouse CD83 protein.

Human peripheral blood mononuclear cells (PBMCs) were isolated using a Ficoll gradient (Ficoll Paque Plus, Pharmacia) and washed with PBS buffer. For activation and proliferation studies, five thousand cells were incubated in 200 μL of media (RPMI, 10%FBS, antibiotics) and 5ug/mL of *Phaseolus vulgaris* leucoagglutinin (PHA) in the presence or absence of increasing concentrations of Protein A purified pre-immune sera or with similarly purified anti-CD83 polyclonal antibodies. After 48 hours at 37°C in a CO_2 incubator the cells were pulsed with [^{3}H] thymidine for ~8 hours and harvested. Thymidine incorporation into the PBMCs was measured using a top counter for analysis.

Results

Figure 16 illustrates that proliferation of PHA-activated human PBMCs was inhibited by antibodies raised against the external region of the mouse CD83 protein. Proliferation of PHA-activated human PBMCs was not affected by addition of increasing concentrations of protein A purified rabbit pre-immune sera. When increasing concentrations of protein A purified rabbit polyclonal sera raised against the mouse CD83 protein was added, a concentration dependent decrease in proliferation was observed.

These data indicate that antibodies raised against the mouse protein are able to cross-react with the human protein. Moreover, antibodies raised against the mouse protein are able to inhibit proliferation of PHA-activated human PBMCs.

All publications, patents and patent applications are incorporated herein by reference. While in the foregoing specification this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

WHAT IS CLAIMED

1. A method of modulating cytokine production in a mammal by modulating the activity or expression of a CD83 polypeptide.

2. A method of modulating cytokine production in a mammal by administering to the mammal an antibody that can modulate the activity or expression of a CD83 polypeptide.

3. A method of modulating cytokine production by a T cell by modulating the activity or expression of a CD83 polypeptide in the T cell.

4. A method of modulating cytokine production by a T cell by contacting the T cell with an antibody that can modulate the activity or expression of a CD83 polypeptide.

5. A method of modulating a CD4+ T cell by modulating the activity or expression of a CD83 polypeptide in the T cell.

6. A method of modulating a CD4+ T cell by contacting the T cell with an antibody that can modulate the activity or expression of a CD83 polypeptide.

7. A method of modulating granulocyte macrophage colony stimulating factor production in a mammal by modulating the activity or expression of CD83 polypeptides.

8. A method of modulating granulocyte macrophage colony stimulating factor production in a mammal by administering to the mammal an antibody that can modulate the activity or expression of CD83 polypeptides.

9. A method of modulating granulocyte macrophage colony stimulating factor production by a T cell by modulating the activity or expression of a CD83 polypeptide in the T cell.

10. A method of modulating granulocyte macrophage colony stimulating factor production by a T cell by contacting the T cell with an antibody that can modulate the activity or expression of a CD83 polypeptide.

11. A method of tumor necrosis factor production in a mammal by modulating the activity or expression of CD83 polypeptides.

12. A method of modulating tumor necrosis factor production in a mammal by administering to the mammal an antibody that can modulate the activity or expression of CD83 polypeptides.

13. A method of inhibiting proliferation of a human peripheral blood mononuclear cell by modulating the activity or expression of CD83 polypeptides.

14. A method of inhibiting proliferation of a human peripheral blood mononuclear cell in a mammal by administering to the mammal an antibody that can modulate the activity or expression of CD83 polypeptides.

15. An antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein activated $CD4^+$ T-cells produce lower levels of interleukin-4 when said T-cells are contacted with the antibody.

16. An antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein $CD4^+$ T-cells proliferation is decreased when said T-cells are contacted with the antibody.

17. An antibody comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID

NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

18. A nucleic acid encoding an antibody comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

19. The nucleic acid of claim 18, wherein the nucleic acid comprises nucleotide sequence SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63 or SEQID NO:65.

20. A method for decreasing the activity of a CD83 gene product, comprising contacting the CD83 gene product with an antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

21. A method for decreasing the activity of a CD83 gene product in a mammal, comprising administering to the mammal an antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

22. A method for decreasing the translation of a CD83 gene product in a mammalian cell, comprising contacting the mammalian cell with a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

23. A method for decreasing the translation of a CD83 gene product in a mammal, comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

24. A method for decreasing proliferation of $CD4^+$ T-cells in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

25. The method of claim 24, wherein the antibody comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ

ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

26. A method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

27. The method of claim 26, wherein the antibody SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

28. A method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

29. The method of claim 26 or 28, wherein the interleukin-2 levels are decreased and the interleukin-4 levels are increased to treat an autoimmune disease.

30. The method of claim 29, wherein the autoimmune disease is diabetes mellitus, arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, multiple sclerosis, myasthenia gravis, systemic

lupus erythematosis, autoimmune thyroiditis, dermatitis, atopic dermatitis, eczematous dermatitis, psoriasis, Sjogren's Syndrome, keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, uveitis posterior, or interstitial lung fibrosis.

31. The method of claim 26 or 28, wherein the interleukin-2 levels are decreased and the interleukin-4 levels are increased to stimulate production of Th2-associated cytokines in transplant recipients.

32. The method of claim 31, wherein the Th2-associated cytokines prolong survival of transplanted tissue.

33. The method of claim 32, wherein the transplanted tissue is skin, cardiac or bone marrow.

34. The method of claim 26 or 28, wherein the mammal is a human.

35. A method for increasing interleukin-10 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

36. The method of claim 35, wherein the antibody comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ

ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

37. A method for increasing interleukin-10 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

38. The method of claim 35 or 37, wherein the interleukin-10 levels are increased to treat neoplastic disease.

39. The method of claim 35 or 37, wherein the interleukin-10 levels are increased to treat a tumor.

40. A method for increasing interleukin-2 levels in a mammal comprising administering to the mammal a functional CD83 polypeptide that comprises SEQ ID NO:9.

41. A method for increasing interleukin-2 levels in a mammal comprising:

(a) transforming a T cell from the mammal with a nucleic acid encoding a functional CD83 polypeptide operably linked to a promoter functional in a mammalian cell, to generate a transformed T cell;

(b) administering the transformed T cell to the mammal to provide increased levels of interleukin-2.

42. The method of claim 41, wherein the CD83 polypeptide comprises SEQ ID NO:9.

43. The method of claim 41, wherein the nucleic acid comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

44. The method of claim 41, wherein the mammal is a human.

45. The method of claim 41, wherein the interleukin-2 levels are increased to treat an allergy or an infectious disease.

46. The method of claim 45, wherein the infectious disease is related to HIV infection, tuberculosis, leishmaniasis, schistosomiasis, filarial nematode infection, or intestinal nematode infection.

47. The method of claim 45, wherein the infectious disease is related to infection by *Aeromonas* spp., *Bacillus* spp., *Bacteroides* spp., *Campylobacter* spp., *Clostridium* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Gastrospirillum* sp., *Helicobacter* spp., *Klebsiella* spp., *Salmonella* spp., *Shigella* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Vibrio* spp., or *Yersinia* spp.

48. The method of claim 45, wherein the infectious disease is related to staph infection, typhus, food poisoning, bascillary dysentery, pneumonia, cholera, an ulcer, diarrhea, hemorrhagic colitis, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura.

49. The method of claim 45, wherein the infectious disease is related to infection by Staphylococcus aureus, Salmonella typhi, Escherichia coli, Escherichia coli O157:H7, Shigella dysenteria, Psuedomonas aerugenosa, Pseudomonas cepacia, Vivrio cholerae, Helicobacter pylori, a multiply-resistant strain of Staphylococcus aureus, a vancomycin-resistant strain of Enterococcus faecium, or a vancomycin-resistant strain of Enterococcus faecalis.

50. The method of claim 45, wherein the infectious disease is related to infection by a virus.

51. The method of claim 50, wherein the virus is a hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, poxvirus, herpes virus, adenovirus, papovavirus, parvovirus, reovirus, orbivirus, picornavirus, rotavirus, alphavirus, rubivirus, influenza virus type A, influenza virus type B, flavivirus, coronavirus, paramyxovirus, morbillivirus, pneumovirus, rhabdovirus, lyssavirus, orthmyxovirus, bunyavirus, phlebovirus, nairovirus, hepadnavirus, arenavirus, retrovirus, enterovirus, rhinovirus or filovirus.

52. A method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

53. The method of claim 52, wherein the antibody comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

54. A method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

55. A method for increasing tumor necrosis factor levels at a selected site in a mammal comprising administering to the site a functional CD83 polypeptide.

56. A method for increasing tumor necrosis factor levels in a selected mammalian cell comprising transforming the cell with a nucleic acid encoding a functional CD83 polypeptide.

57. The method of claim 55 or 56, wherein the mammal is human and the CD83 polypeptide comprises SEQ ID NO:9.

58. A method of identifying a compound that can modulate CD4+T cell activation comprising administering a test compound to a mutant mouse and observing whether CD4+ T cells become activated, wherein the somatic and germ cells of the mutant mouse comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8.

59. A mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8.

60. The mutant CD83 gene of claim 63 comprising nucleotide sequence SEQ ID NO:3.

61. A mutant mouse whose somatic and germ cells comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8, wherein expression of said mutant CD83 gene reduces CD4+T cell activation.

62. The mutant mouse of claim 61, wherein the mutant CD83 gene comprises SEQ ID NO:3.

	Mom	G3 ID	% CD4+
Pedigree 57	G2 # 1	57.1.1	22
		57.1.2	26
		57.1.3	24
	G2 # 4	57.4.1	15
		57.4.2	18
	G2 # 5	57.5.1	21
		57.5.2	19
		57.5.3	24
		57.5.4	22
		57.5.5	19
		57.5.6	17
Pedigree 9	G2 # 4	9.4.1	6
		9.4.2	20
		9.4.3	16
		9.4.4	12
		9.4.5	20
		9.4.6	15
		9.4.7	24
		9.4.8	27
		9.4.9	5
	G2 # 5	9.5.1	18
		9.5.2	20
		9.5.3	22
		9.5.4	20
		9.5.5	22
		9.5.6	20
		9.5.7	23

average	19.1
stdev	5.2
= + 2SD	29.6
= -2SD	8.7

FIG. 1

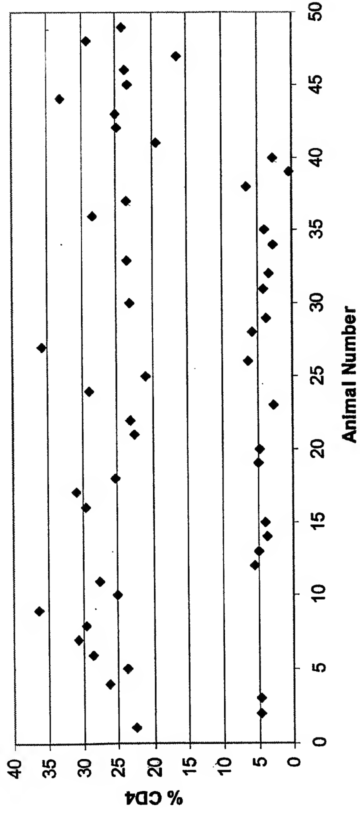
% CD4
40
35
30
25
20
15
10
5
0
Animal Number
0
5
10
15
20
25
30
35
40
45
50

FIG. 2

1 GCGCTCCAGC CGC**<u>ATG</u>**TCGC AAGGCCTCCA GCTCCTGTTT CTAGGCTGCG
51 CCTGCAGCCT GGCACCCGCG ATGGCGATGC GGGAGGTGAC GGTGGCTTGC
101 TCCGAGACCG CCGACTTGCC TTGCACAGCG CCCTGGGACC CGCAGCTCTC
151 CTATGCAGTG TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC CAGGAGAAGG
251 GCCTATTCCC TGACGATCCA AAACACTACC ATCTGCAGCT CGGGCACCTA
301 CAGGTGTGCC CTGCAGGAGC TCGGAGGGCA GCGCAACTTG AGCGGCACCG
351 TGGTTCTGAA GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC
401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG TTGTTTTCTA
451 CCTGACACTC ATCATTTTCA CCTGCAAATT TGCACGACTA CAAAGCATTT
501 TCCCAGATAT TTCTAAACCT GGTACGGAAC AAGCTTTTCT TCCAGTCACC
551 TCCCCAAGCA AACATTTGGG GCCAGTGACC CTTCCTAAGA CAGAAACGGT
601 A**<u>TGA</u>**GTAGGA TCTCCACTGG TTTTTACAAA GCCAAGGGCA CATCAGATCA
651 GTGTGCCTGA ATGCCACCCG GACAAGAGAA GAATGAGCTC CATCCTCAGA
701 TGGCAACCTT TCTTTGAAGT CCTTCACCTG ACAGTGGGCT CCACACTACT
751 CCCTGACACA GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA
801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG GCTATCTGGT
851 CAACCTCGTG AGTGCTTTTC AGTCATCTAC AAGCTATGGT GAGATGCAGG
901 TGAAGCAGGG TCATGGGAAA TTTGAACACT CTGAGCTGGC CCTGTGACAG
951 ACTCCTGAGG ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA
1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC TGGCGGAAAT
1051 TGACAGGCCA AGCTGTGAGC CAGTGGGAAA TATTTAGCAA ATAATTTCCC
1101 AGTGCGAAGG TCCTGCTATT AGTAAGGAGT ATTATGTGTA CATAGAAATG
1151 AGAGGTCAGT GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA
1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT TTTTAATCTT
1251 CATGTACTTG TCAAAGAAGA ATTTTTCATG TTTTTTCAAA GAAGTGTGTT
1301 TCTTTCCTTT TTTAAAATAT GAAGGTCTAG TTACATAGCA TTGCTAGCTG
1351 ACAAGCAGCC TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA
1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA CAATGGACTG
1451 AGAAACCAGA AGTCTGGCCA CAAGATTGTC TGTATGATTC TGGACGAGTC
1501 ACTTGTGGTT TTCACTCTCT GGTTAGTAAA CCAGATAGTT TAGTCTGGGT
1551 TGAATACAAT GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT AGAGTTCTGG
1651 AGCTGAGCGA ATGCCTGTCA TATCTCAGCT TGCCCATCAA TCCAAACACA
1701 GGAGGCTACA AAAAGGACAT GAGCATGGTC TTCTGTGTGA ACTCCTCCTG
1751 AGAAACGTGG AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG ACAGGAGGAA
1851 GTTCTCAGAT GTTGCATTGA TGTAACATTG TTGCATTTCT TTAATGAGCT
1901 GGGCTCCTTC CTCATTTGCT TCCCAAAGAG ATTTGTCCCC ACTAATGGTG
1951 TGCCCATCAC CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA ATGCATGTGA
2051 A

FIG. 3

```
1     GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTTT CTAGGCTGCG
51    CCTGCAGCCT GGCACCCGCG ATGGCGATGC GGGAGGTGAC GGTGGCTTGC
101   TCCGAGACCG CCGACTTGCC TTGCACAGCG CCCTGGGACC CGCAGCTCTC
151   CTATGCAGTG TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
201   AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC CAGGAGAAGG
251   GCCTATTCCC TGACGATCCA AAACACTACC ATCTGCAGCT CGGGCACCTA
301   CAGGTGTGCC CTGCAGGAGC TCGGAGGGCA GCGCAACTTG AGCGGCACCG
351   TGGTTCTGAA GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC
401   AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG TTGTTTTCTA
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501   TCCCAGATAT TTCTAAACCT GGTACGGAAC AAGCTTTTCT TCCAGTCACC
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651   GTGTGCCTGA ATGCCACCCG GACAAGAGAA GAATGAGCTC CATCCTCAGA
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751   CCCTGACACA GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA
801   TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG GCTATCTGGT
851   CAACCTCGTG AGTGCTTTTC AGTCATCTAC AAGCTATGGT GAGATGCAGG
901   TGAAGCAGGG TCATGGGAAA TTTGAACACT CTGAGCTGGC CCTGTGACAG
951   ACTCCTGAGG ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA
1001  TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC TGGCGGAAAT
1051  TGACAGGCCA AGCTGTGAGC CAGTGGGAAA TATTTAGCAA ATAATTTCCC
1101  AGTGCGAAGG TCCTGCTATT AGTAAGGAGT ATTATGTGTA CATAGAAATG
1151  AGAGGTCAGT GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA
1201  TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT TTTTAATCTT
1251  CATGTACTTG TCAAAGAAGA ATTTTTCATG TTTTTTCAAA GAAGTGTGTT
```

FIG. 4A

1301 TCTTTCCTTT TTTAAAATAT GAAGGTCTAG TTACATAGCA TTGCTAGCTG
1351 ACAAGCAGCC TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA
1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA CAATGGACTG
1451 AGAAACCAGA AGTCTGGCCA CAAGATTGTC TGTATGATTC TGGACGAGTC
1501 ACTTGTGGTT TTCACTCTCT GGTTAGTAAA CCAGATAGTT TAGTCTGGGT
1551 TGAATACAAT GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT AGAGTTCTGG
1651 AGCTGAGCGA ATGCCTGTCA TATCTCAGCT TGCCCATCAA TCCAAACACA
1701 GGAGGCTACA AAAAGGACAT GAGCATGGTC TTCTGTGTGA ACTCCTCCTG
1751 AGAAACGTGG AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG ACAGGAGGAA
1851 GTTCTCAGAT GTTGCATTGA TGTAACATTG TTGCATTTCT TTAATGAGCT
1901 GGGCTCCTTC CTCATTTGCT TCCCAAAGAG ATTTTGTCCC ACTAATGGTG
1951 TGCCCATCAC CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA ATGCATGTGA
2051 A

FIG. 4B

Wild Type Amino Acid Sequence for CD83 protein [Mus musculus]

MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP WDPQLSYAVS
WAKVSESGTE SVELPESKQN SSFEAPRRRA YSLTIQNTTI CSSGTYRCAL
QELGGQRNLS GTVVLKVTGC PKEATESTFR KYRAEAVLLF SLVVFYLTLI
IFTCKFARLQ SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETV

Mutant CD83 Amino Acid Sequence: novel tail underlined, in bold.

MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP WDPQLSYAVS
WAKVSESGTE SVELPESKQN SSFEAPRRRA YSLTIQNTTI CSSGTYRCAL
QELGGQRNLS GTVVLKVTGC PKEATESTFR KYRAEAVLLF SLVVFYLTLI
IFTCKFARLQ SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETV**RVGS**
PLVFTKPRAH QISVPECHPD KRRMSSILRW QPFFEVLHLT VGSTLLPDTG
S

FIG. 5

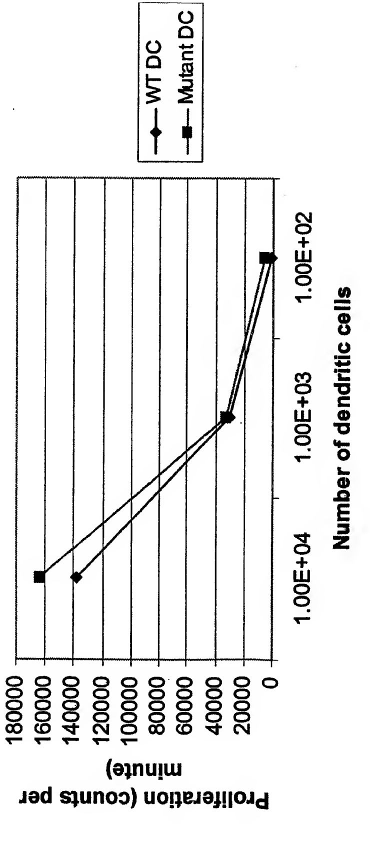

WT DC
Mutant DC
Proliferation (counts per minute)
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
1.00E+04
1.00E+03
1.00E+02
Number of dendritic cells

FIG. 6A

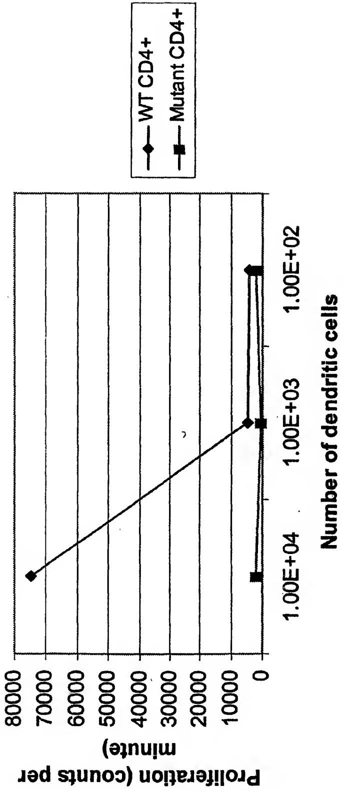

WT CD4+
Mutant CD4+
Proliferation (counts per minute)
80000
70000
60000
50000
40000
30000
20000
10000
0
1.00E+04
1.00E+03
1.00E+02
Number of dendritic cells

FIG. 6B

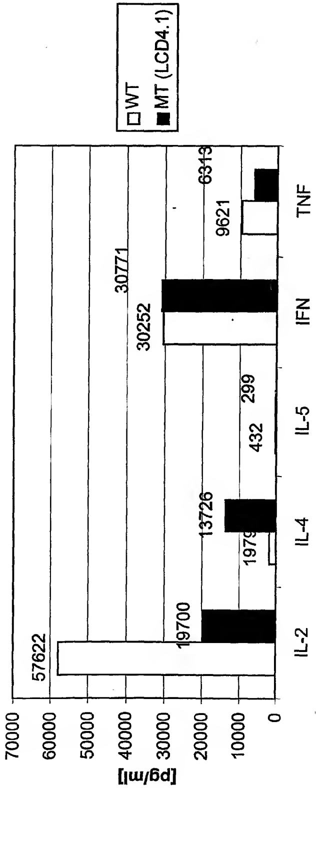

WT
MT (LCD4.1)
[pg/ml]
70000
60000
50000
40000
30000
20000
10000
0
57622
19700
1979
13726
432
299
30252
30771
9621
6313
IL-2
IL-4
IL-5
IFN
TNF

FIG. 7

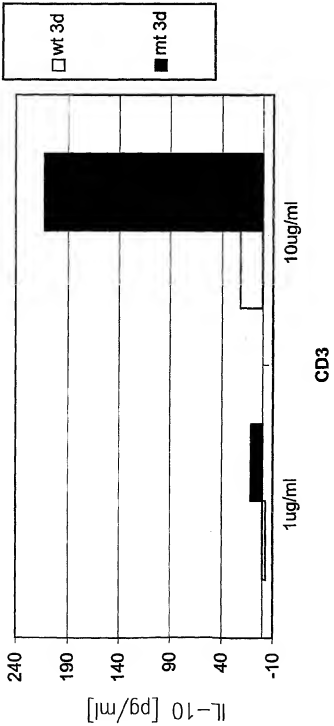


FIG. 8

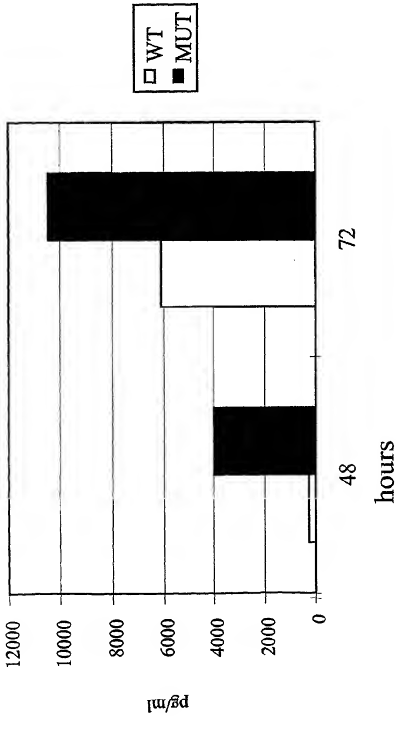


FIG. 9

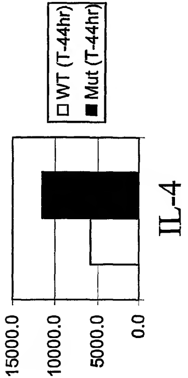


FIG. 10A

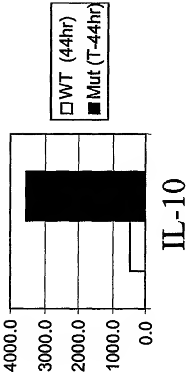
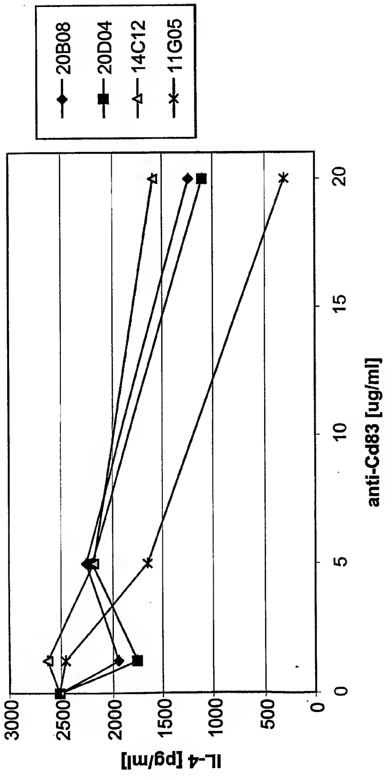


FIG. 10B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20D04
14C12
11G05
IL-4 [pg/ml]
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
anti-Cd83 [ug/ml]

FIG. 11

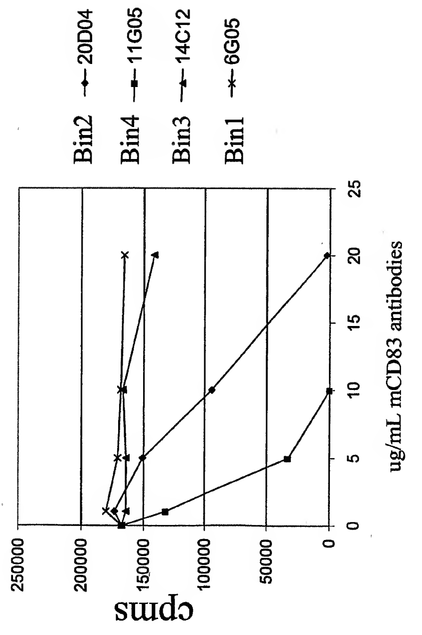

cpms
250000
200000
150000
100000
50000
0
0
5
10
15
20
25
ug/mL mCD83 antibodies
Bin2 20D04
Bin4 11G05
Bin3 14C12
Bin1 6G05

FIG. 12

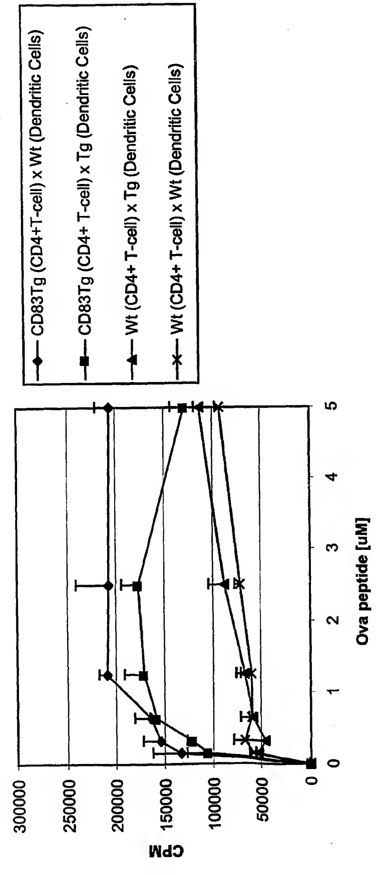

CD83Tg (CD4+T-cell) x Wt (Dendritic Cells)
CD83Tg (CD4+ T-cell) x Tg (Dendritic Cells)
Wt (CD4+ T-cell) x Tg (Dendritic Cells)
Wt (CD4+ T-cell) x Wt (Dendritic Cells)
CPM
300000
250000
200000
150000
100000
50000
0
0
1
2
3
4
5
Ova peptide [uM]

FIG. 13

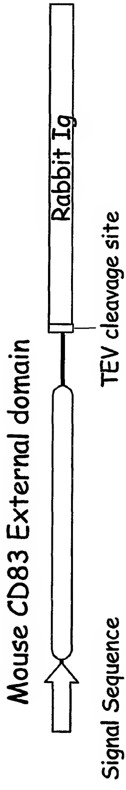

Mouse CD83 External domain
Rabbit Ig
TEV cleavage site
Signal Sequence

FIG. 14

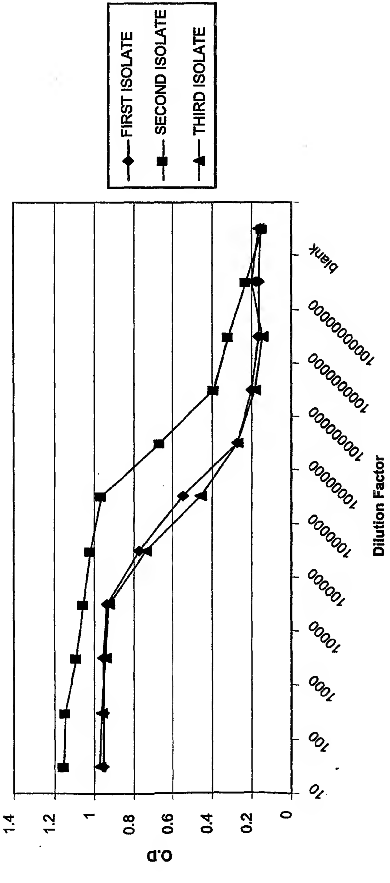
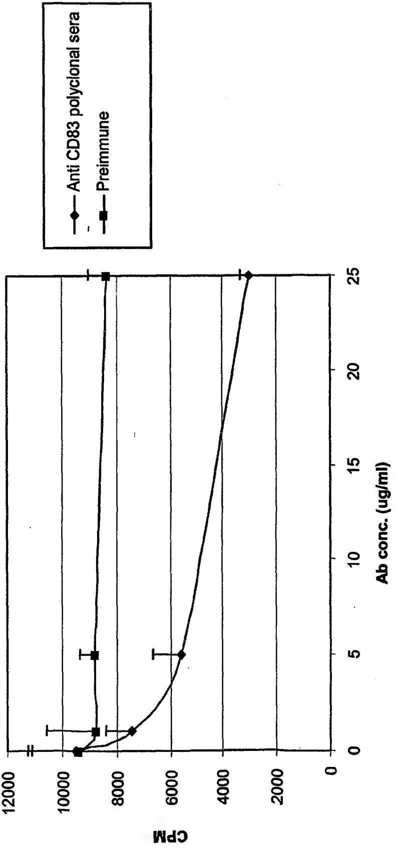

FIRST ISOLATE
SECOND ISOLATE
THIRD ISOLATE
O.D
1.4
1.2
1
0.8
0.6
0.4
0.2
0
10
100
1000
10000
100000
1000000
10000000
100000000
1000000000
10000000000
blank
Dilution Factor

FIG. 15



Anti CD83 polyclonal sera
Preimmune
CPM
12000
10000
8000
6000
4000
2000
0
0
5
10
15
20
25
Ab conc. (ug/ml)

FIG. 16

	CDR1 / CDR2
20B08H	METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGF**SLSSYDMT**WVRQAPGKGLEWIGII**YAS-**
6G05H	METGLRWLLLVAVLKGVQCQSVEESGGRLVSPGTPLTLTCTASGFSLS**SYDMS**WVRQAPGKGLEYIGII**SSS-**
20D04H	METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLS**SYDMS**WVRQAPGKGLEWIGII**YAS-**
11G05	METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFTIS**DYDLS**WVRQAPGEGLKYIGFI**AID-**
14C12	METGLRWLLLVAVLKGVHCQSVEESGGRLVTPGTPLTLTCTASGFSRS**SYDMS**WVRQAPGKGLEWVGVI**STA-**

	CDR3
20B08H	**GSTYY**ASWAKGRFTISKTSTTVDLEVTSLTTEDTATYFCSR**EHAGYSGDTGH**LWGPGTLVTVSSGQPKAPSVF
6G05H	**GTTYY**ANWAKGRFTISKTSTTVDLKVTSPTIGDTATYFCAR**EGAGVSMT---**LWGPGTLVTVSSGQPKAPSVF
20D04H	**GSTYY**ASWAKGRVAISKTSTTVDLKITSPTTEDTATYFCAR**EDAGFSNA---**LWGPGTLVTVSSGQPKAPSVF
11G05	**GNPYY**ATWAKGRFTISKTSTTVDLKITAPTTEDTATYFCAR**GAGD-------**LWGPGTLVTVSSGQPKAPSVF
14C12	**YNSHY**ASWAKGRFTISRTSTTVDLKMTSLTTEDTATYFCAR**GGSWLD-----**LWGQGTLVTVSSGQPKAPSVF

20B08H	PLAPCCGDTPSS
6G05H	PLAPCCGDTPSS
20D04H	PLAPCCGDTPSS
11G05	PLAPCCGDTPSS
14C12	PLAPCCGDTPSS

FIG. 17A

CDR1 CDR2

20B08L MDMRAPTQLLGLLLLWLPGA**RC-AYD**MTQTPASVEVAVGGTVTIKCQAS**QSISTY**--
6G05L MDMRAPTQLLGLLLLWLPGA**RC-AYD**MTQTPASVEVAVGGTVAIKCQAS**QSVSSY**--
20D04L MDMRAPTQLLGLLLLWLPGA**RCADVV**MTQTPASVSAAVGGTVTINCQAS**ESISNY**--
11G05L MDTRAPTQLLGLLLLWLPGA**RCADVV**MTQTPASVSAAVGGTVTINCQSS**KNVYNNNW**
14C12L MDXRAPTQLLGLLLLWLPGA**RCA-LV**MTQTPASVSAAVGGTVTINCQSS**QSVYDNDE**

CDR3

20B08L LDWYQQKPGQPPKLLIYDASDLASGVPSRFKGSGSGTQFTLTISDLECADAATYYC**QQGYT**---
6G05L LAWYQQKPGQPPKPLIYEASMLAAGVSSRFKGSGSGTDFTLTISDLECDDAATYYC**QQGYS**---
20D04L LSWYQQKPGQPPKLLIYRTSTLASGVSSRFKGSGSGTEYTLTISGVQCDDVATYYC**QCTSGG**-
11G05L LSWFQQKPGQPPKLLIYYASTLASGVPSRFRGSGSGTQFTLTISDVQCDDAATYYC**AG-DYSS--S**
14C12L LSWYQQKPGQPPKLLIYLASKLASGVPSRFKGSGSGTQFALTISGVQCDDAATYYC**QATHYSS--D-**

20B08L -**HSNVDNV**FGGGTEVVVKGDPVAPTVLLFPPSS
6G05L -**ISDIDNA**FGGGTEVVVKGDPVAPTVLLFPPSS
20D04L **KFISDGAA**FGGGTEVVVKGDPVAPTVLLFPPSS
11G05L **SDNG**FGGGTEVVVKGDPVAPTVLLFPPSS
14C12L - **WYLT**FGGGTEVVVKGDPVAPTVLLFPPSS

FIG. 17B

SEQUENCE LISTING

<110> Appleby, MW
Proll, S
Paeper, B
Staehling-Hampton, K

<120> MANIPULATION OF CYTOKINE LEVELS USING CD83 GENE PRODUCTS

<130> 1427.004WO1

<150> US 60/331,958
<151> 2001-11-21

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<213> Mus musculus

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35 40 45
Val Ser Trp Ala Lys Val Ser Glu Ser Gly Thr Glu Ser Val Glu Leu
50 55 60
Pro Glu Ser Lys Gln Asn Ser Ser Phe Glu Ala Pro Arg Arg Arg Ala
65 70 75 80
Tyr Ser Leu Thr Ile Gln Asn Thr Thr Ile Cys Ser Ser Gly Thr Tyr
85 90 95
Arg Cys Ala Leu Gln Glu Leu Gly Gly Gln Arg Asn Leu Ser Gly Thr
100 105 110
Val Val Leu Lys Val Thr Gly Cys Pro Lys Glu Ala Thr Glu Ser Thr
115 120 125
Phe Arg Lys Tyr Arg Ala Glu Ala Val Leu Leu Phe Ser Leu Val Val
130 135 140
Phe Tyr Leu Thr Leu Ile Ile Phe Thr Cys Lys Phe Ala Arg Leu Gln

145 150 155 160

Ser Ile Phe Pro Asp Ile Ser Lys Pro Gly Thr Glu Gln Ala Phe Leu

165 170 175

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tccagtcacc tccccaagca aacatttggg gccagtgacc cttcctaaga cagaaacggt     600
aagagtagga tctccactgg tttttacaaa gccaagggca catcagatca gtgtgcctga     660
atgccacccg gacaagagaa gaatgagctc catcctcaga tggcaacctt tctttgaagt     720
ccttcacctg acagtgggct ccacactact ccctgacaca gggtcttgag caccatcata     780
tgatcacgaa gcatggagta tcaccgcttc tctgtggctg tcagcttaat gtttcatgtg     840
gctatctggt caacctcgtg agtgcttttc agtcatctac aagctatggt gagatgcagg     900
tgaagcaggg tcatgggaaa tttgaacact ctgagctggc cctgtgacag actcctgagg     960
acagctgtcc tctcctacat ctgggataca tctctttgaa tttgtcctgt ttcgttgcac    1020
cagcccagat gtctcacatc tggcggaaat tgacaggcca agctgtgagc cagtgggaaa    1080
tatttagcaa ataatttccc agtgcgaagg tcctgctatt agtaaggagt attatgtgta    1140
catagaaatg agaggtcagt gaactattcc ccagcagggc cttttcatct ggaaaagaca    1200
tccacaaaag cagcaataca gagggatgcc acatttattt ttttaatctt catgtacttg    1260
tcaaagaaga atttttcatg ttttttcaaa gaagtgtgtt tctttccttt tttaaaatat    1320
gaaggtctag ttacatagca ttgctagctg acaagcagcc tgagagaaga tggagaatgt    1380
tcctcaaaat agggacagca agctagaagc actgtacagt gccctgctgg gaagggcaga    1440
caatggactg agaaaccaga agtctggcca caagattgtc tgtatgattc tggacgagtc    1500
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acttgtggtt ttcactctct ggttagtaaa ccagatagtt tagtctgggt tgaatacaat    1560
ggatgtgaag ttgcttgggg aaagctgaat gtagtgaata cattggcaac tctactgggc    1620
tgttaccttg ttgatatcct agagttctgg agctgagcga atgcctgtca tatctcagct    1680
tgcccatcaa tccaaacaca ggaggctaca aaaggacat gagcatggtc ttctgtgtga    1740
actcctcctg agaaacgtgg agactggctc agcgctttgc gcttgaagga ctaatcacaa    1800
gttcttgaag atatggacct aggggagcta ttgcgccacg acaggaggaa gttctcagat    1860
gttgcattga tgtaacattg ttgcatttct ttaatgagct gggctccttc ctcatttgct    1920
tcccaaagag attttgtccc actaatggtg tgcccatcac ccacactatg aaagtaaaag    1980
ggatgctgag cagatacagc gtgcttacct ctcagccatg actttcatgc tattaaaaga    2040
atgcatgtga a                                                         2051
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<210> 4
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutant CD83 sequence

<400> 4

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Met Ser Gln Gly Leu Gln Leu Leu Phe Leu Gly Cys Ala Cys Ser Leu
1               5                   10                  15
Ala Pro Ala Met Ala Met Arg Glu Val Thr Val Ala Cys Ser Glu Thr
            20                  25                  30
Ala Asp Leu Pro Cys Thr Ala Pro Trp Asp Pro Gln Leu Ser Tyr Ala
        35                  40                  45
Val Ser Trp Ala Lys Val Ser Glu Ser Gly Thr Glu Ser Val Glu Leu
    50                  55                  60
Pro Glu Ser Lys Gln Asn Ser Ser Phe Glu Ala Pro Arg Arg Arg Ala
65                  70                  75                  80
Tyr Ser Leu Thr Ile Gln Asn Thr Thr Ile Cys Ser Ser Gly Thr Tyr
                85                  90                  95
Arg Cys Ala Leu Gln Glu Leu Gly Gly Gln Arg Asn Leu Ser Gly Thr
            100                 105                 110
Val Val Leu Lys Val Thr Gly Cys Pro Lys Glu Ala Thr Glu Ser Thr
        115                 120                 125
Phe Arg Lys Tyr Arg Ala Glu Ala Val Leu Leu Phe Ser Leu Val Val
    130                 135                 140
Phe Tyr Leu Thr Leu Ile Ile Phe Thr Cys Lys Phe Ala Arg Leu Gln
145                 150                 155                 160
Ser Ile Phe Pro Asp Ile Ser Lys Pro Gly Thr Glu Gln Ala Phe Leu
                165                 170                 175
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Pro Val Thr Ser Pro Ser Lys His Leu Gly Pro Val Thr Leu Pro Lys
180 185 190
Thr Glu Thr Val Arg Val Gly Ser Pro Leu Val Phe Thr Lys Pro Arg
195 200 205
Ala His Gln Ile Ser Val Pro Glu Cys His Pro Asp Lys Arg Arg Met
210 215 220
Ser Ser Ile Leu Arg Trp Gln Pro Phe Phe Glu Val Leu His Leu Thr
225 230 235 240
Val Gly Ser Thr Leu Leu Pro Asp Thr Gly Ser
245 250

<210> 5
<211> 756
<212> DNA
<213> Artificial Sequence

<220>
<223> Mutant CD83 sequence

<400> 5
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gcgatgcggg aggtgacggt ggcttgctcc gagaccgccg acttgccttg cacagcgccc 120
tgggacccgc agctctccta tgcagtgtcc tgggccaagg tctccgagag tggcactgag 180
agtgtggagc tcccggagag caagcaaaac agctccttcg aggcccccag gagaagggcc 240
tattccctga cgatccaaaa cactaccatc tgcagctcgg gcacctacag gtgtgccctg 300
caggagctcg gagggcagcg caacttgagc ggcaccgtgg ttctgaaggt gacaggatgc 360
cccaaggaag ctacagagtc aactttcagg aagtacaggg cagaagctgt gttgctcttc 420
tctctggttg ttttctacct gacactcatc attttcacct gcaaatttgc acgactacaa 480
agcattttcc cagatatttc taaacctggt acggaacaag cttttcttcc agtcacctcc 540
ccaagcaaac atttggggcc agtgaccctt cctaagacag aaacggtaag agtaggatct 600
ccactggttt ttacaaagcc aagggcacat cagatcagtg tgcctgaatg ccacccggac 660
aagagaagaa tgagctccat cctcagatgg caacctttct ttgaagtcct tcacctgaca 720
gtgggctcca cactactccc tgacacaggg tcttga 756

<210> 6

<400> 6
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<210> 7
<211> 168
<212> DNA

<213> Artificial Sequence

<220>
<223> Mutant CD83 sequence

<400> 7
agagtaggat ctccactggt ttttacaaag ccaagggcac atcagatcag tgtgcctgaa 60
tgccacccgg acaagagaag aatgagctcc atcctcagat ggcaaccttt ctttgaagtc 120
cttcacctga cagtgggctc cacactactc cctgacacag ggtcttga 168

<210> 8
<211> 55
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutant CD83 sequence

<400> 8
Arg Val Gly Ser Pro Leu Val Phe Thr Lys Pro Arg Ala His Gln Ile
1 5 10 15
Ser Val Pro Glu Cys His Pro Asp Lys Arg Arg Met Ser Ser Ile Leu
20 25 30
Arg Trp Gln Pro Phe Phe Glu Val Leu His Leu Thr Val Gly Ser Thr
35 40 45
Leu Leu Pro Asp Thr Gly Ser
50 55

<210> 9
<211> 205
<212> PRT
<213> Homo sapiens

<400> 9
Met Ser Arg Gly Leu Gln Leu Leu Leu Leu Ser Cys Ala Tyr Ser Leu
1 5 10 15
Ala Pro Ala Thr Pro Glu Val Lys Val Ala Cys Ser Glu Asp Val Asp
20 25 30
Leu Pro Cys Thr Ala Pro Trp Asp Pro Gln Val Pro Tyr Thr Val Ser
35 40 45
Trp Val Lys Leu Leu Glu Gly Gly Glu Glu Arg Met Glu Thr Pro Gln
50 55 60

Glu Asp His Leu Arg Gly Gln His Tyr His Gln Lys Gly Gln Asn Gly
65 70 75 80

Ser Phe Asp Ala Pro Asn Glu Arg Pro Tyr Ser Leu Lys Ile Arg Asn
85 90 95

Thr Thr Ser Cys Asn Ser Gly Thr Tyr Arg Cys Thr Leu Gln Asp Pro
100 105 110

Asp Gly Gln Arg Asn Leu Ser Gly Lys Val Ile Leu Arg Val Thr Gly
115 120 125

Cys Pro Ala Gln Arg Lys Glu Glu Thr Phe Lys Lys Tyr Arg Ala Glu
130 135 140

Ile Val Leu Leu Leu Ala Leu Val Ile Phe Tyr Leu Thr Leu Ile Ile
145 150 155 160

Phe Thr Cys Lys Phe Ala Arg Leu Gln Ser Ile Phe Pro Asp Phe Ser
165 170 175

Lys Ala Gly Met Glu Arg Ala Phe Leu Pro Val Thr Ser Pro Asn Lys
180 185 190

His Leu Gly Leu Val Thr Pro His Lys Thr Glu Leu Val
195 200 205

<210> 10
<211> 2574
<212> DNA
<213> Homo sapiens

<400> 10
cctggcgcag ccgcagcagc gacgcgagcg aactcggccg ggcccgggcg cgcgggggcg 60
ggacgcgcac gcggcgaggg cggcgggtga gccgggggcg gggacggggg cgggacgggg 120
gcgaaggggg cggggacggg ggcgcccgcc ggcctaacgg gattaggagg gcgcgccacc 180
cgcttccgct gcccgccggg gaatccccg ggtggcgccc agggaagttc ccgaacgggc 240
gggcataaaa gggcagccgc gccggcgccc cacagctctg cagctcgtgg cagcggcgca 300
gcgctccagc catgtcgcgc ggcctccagc ttctgctcct gagctgcgcc tacagcctgg 360
ctcccgcgac gccggaggtg aaggtggctt gctccgaaga tgtggacttg ccctgcaccg 420
ccccctggga tccgcaggtt ccctacacgg tctcctgggt caagttattg gagggtggtg 480
aagagaggat ggagacaccc caggaagacc acctcagggg acagcactat catcagaagg 540
ggcaaaatgg ttctttcgac gcccccaatg aaaggcccta ttccctgaag atccgaaaca 600
ctaccagctg caactcgggg acatacaggt gcactctgca ggacccggat gggcagagaa 660
acctaagtgg caaggtgatc ttgagagtga caggatgccc tgcacagcgt aaagaagaga 720
cttttaagaa atacagagcg gagattgtcc tgctgctggc tctggttatt ttctacttaa 780
cactcatcat tttcacttgt aagtttgcac ggctacagag tatcttccca gatttttcta 840
aagctggcat ggaacgagct tttctcccag ttacctcccc aaataagcat ttagggctag 900
tgactcctca caagacagaa ctggtatgag caggatttct gcaggttctt cttcctgaag 960
ctgaggctca ggggtgtgcc tgtctgttac actggaggag agaagaatga gcctacgctg 1020

aagatggcat cctgtgaagt ccttcacctc actgaaaaca tctggaaggg gatcccaccc 1080
cattttctgt gggcaggcct cgaaaaccat cacatgacca catagcatga ggccactgct 1140
gcttctccat ggccaccttt tcagcgatgt atgcagctat ctggtcaacc tcctggacat 1200
tttttcagtc atataaaagc tatggtgaga tgcagctgga aaagggtctt gggaaatatg 1260
aatgcccccca gctggcccgt gacagactcc tgaggacagc tgtcctcttc tgcatcttgg 1320
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gaaattgaca gatcaagctg tgagacagtg ggaaatattt agcaaataat ttcctggtgt 1440
gaaggtcctg ctattactaa ggagtaatct gtgtacaaag aaataacaag tcgatgaact 1500
attccccagc agggtctttt catctgggaa agacatccat aaagaagcaa taaagaagag 1560
tgccacattt atttttatat ctatatgtac ttgtcaaaga aggtttgtgt ttttctgctt 1620
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agggagaaga agtcagagag ggtgacaaga tagagagcta tttaatggcc ggctggaaat 1740
gctgggctga cggtgcagtc tgggtgctcg cccacttgtc ccactatctg ggtgcatgat 1800
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cgaaactcca ttgagtcatt atccttgcta tgatgatggt gttttgggga tgagagggtg 1980
ctatccattt ctcatgtttt ccattgtttg aaacaaagaa ggttaccaag aagcctttcc 2040
tgtagccttc tgtaggaatt cttttgggga agtgaggaag ccaggtccac ggtctgttct 2100
tgaagcagta gcctaacaca ctccaagata tggacacacg ggagccgctg gcagaaggga 2160
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cccttccctt cttggtttcc aaaggcattt attgctgagt tatatgttca ctgtcccccct 2280
aatattaggg agtaaaacgg ataccaagtt gatttagtgt ttttacctct gtcttggctt 2340
tcatgttatt aaacgtatgc atgtgaagaa gggtgttttt ctgttttata ttcaactcat 2400
aagactttgg gataggaaaa atgagtaatg gttactaggc ttaatacctg ggtgattaca 2460
taatctgtac aacgaacccc catgatgtaa gtttacctat gtaacaaacc tgcacttata 2520
cccatgaact taaaatgaaa gttaaaaata aaaaacatat acaaataaaa aaaa 2574

<210> 11
<211> 239
<212> PRT
<213> Oryctolagus cuniculus

<400> 11
Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala
20 25 30
Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala
35 40 45
Ser Glu Ser Ile Ser Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly
50 55 60
Gln Pro Pro Lys Leu Leu Ile Tyr Arg Thr Ser Thr Leu Ala Ser Gly

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65                  70                  75                  80
Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu
                85                  90                  95
Thr Ile Ser Gly Val Gln Cys Asp Asp Val Ala Thr Tyr Tyr Cys Gln
            100                 105                 110
Cys Thr Ser Gly Gly Lys Phe Ile Ser Asp Gly Ala Ala Phe Gly Gly
        115                 120                 125
Gly Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu
    130                 135                 140
Leu Phe Pro Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile
145                 150                 155                 160
Val Cys Val Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu
                165                 170                 175
Val Asp Gly Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro
            180                 185                 190
Gln Asn Ser Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu
        195                 200                 205
Thr Ser Thr Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr
    210                 215                 220
Gln Gly Thr Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys
225                 230                 235
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<210> 12
<211> 720
<212> DNA
<213> Oryctolagus cuniculus

<400> 12

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agatgtgccg atgtcgtgat gacccagact ccagcctccg tgtctgcagc tgtgggaggc     120
acagtcacca tcaattgcca ggccagtgaa agcattagca actacttatc ctggtatcag     180
cagaaaccag ggcagcctcc caagctcctg atctacagga catccactct ggcatctggg     240
gtctcatcgc ggttcaaagg cagtggatct gggacagagt acactctcac catcagcggc     300
gtgcagtgtg acgatgttgc cacttactac tgtcaatgca cttctggtgg gaagttcatt     360
agtgatggtg ctgctttcgg cggagggacc gaggtggtgg tcaaaggtga tccagttgca     420
cctactgtcc tcctcttccc accatctagc gatgaggtgg caactggaac agtcaccatc     480
gtgtgtgtgg cgaataaata ctttcccgat gtcaccgtca cctgggaggt ggatggcacc     540
acccaaacaa ctggcatcga gaacagtaaa acaccgcaga attctgcaga ttgtacctac     600
aacctcagca gcactctgac actgaccagc acacagtaca acagccacaa agagtacacc     660
tgcaaggtga cccagggcac gacctcagtc gtccagagct tcagtaggaa gaactgttaa     720
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<210> 13

<211> 454
<212> PRT
<213> Oryctolagus cuniculus

<400> 13

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
 1               5                  10                  15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
        35                  40                  45
Asn Asn Ala Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60
Trp Ile Gly Tyr Ile Trp Ser Gly Gly Leu Thr Tyr Tyr Ala Asn Trp
65                  70                  75                  80
Ala Glu Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95
Lys Met Thr Ser Pro Thr Ile Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110
Arg Gly Ile Asn Asn Ser Ala Leu Trp Gly Pro Gly Thr Leu Val Thr
        115                 120                 125
Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro
    130                 135                 140
Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys Leu Val
145                 150                 155                 160
Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Thr
                165                 170                 175
Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser Ser Gly
            180                 185                 190
Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser Gln Pro
        195                 200                 205
Val Thr Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val Asp Lys
    210                 215                 220
Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro Pro Glu
225                 230                 235                 240
Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270
Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile Asn Asn
        275                 280                 285
Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln Phe Asn
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290 295 300
Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp
305 310 315 320
Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro
325 330 335
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu
340 345 350
Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg
355 360 365
Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile
370 375 380
Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr
385 390 395 400
Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys
405 410 415
Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys
420 425 430
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile
435 440 445
Ser Arg Ser Pro Gly Lys
450

<210> 14
<211> 1362
<212> DNA
<213> Oryctolagus cuniculus

<400> 14
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tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120
accgtctctg gattctccct cagtaacaat gcaataaact gggtccgcca ggctccaggg 180
aaggggctag agtggatcgg atacatttgg agtggtgggc ttacatacta cgcgaactgg 240
gcggaaggcc gattcaccat ctccaaaacc tcgactacgg tggatctgaa gatgaccagt 300
ccgacaatcg aggacacggc cacctatttc tgtgccagag ggattaataa ctccgctttg 360
tggggcccag gcaccctggt caccgtctcc tcagggcaac ctaaggctcc atcagtcttc 420
ccactggccc cctgctgcgg ggacacaccc tctagcacgg tgaccttggg ctgcctggtc 480
aaaggctacc tcccggagcc agtgaccgtg acctggaact cgggcaccct caccaatggg 540
gtacgcacct tcccgtccgt ccggcagtcc tcaggcctct actcgctgag cagcgtggtg 600
agcgtgacct caagcagcca gcccgtcacc tgcaacgtgg cccacccagc caccaacacc 660
aaagtggaca agaccgttgc gccctcgaca tgcagcaagc ccacgtgccc accccctgaa 720
ctcctggggg gaccgtctgt cttcatcttc cccccaaaac ccaaggacac cctcatgatc 780
tcacgcaccc ccgaggtcac atgcgtggtg gtggacgtga gccaggatga ccccgaggtg 840

cagttcacat ggtacataaa caacgagcag gtgcgcaccg cccggccgcc gctacgggag 900
cagcagttca acagcacgat ccgcgtggtc agcaccctcc ccatcgcgca ccaggactgg 960
ctgaggggca aggagttcaa gtgcaaagtc cacaacaagg cactcccggc ccccatcgag 1020
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ccccgggagg agctgagcag caggtcggtc agcctgacct gcatgatcaa cggcttctac 1140
ccttccgaca tctcggtgga gtgggagaag aacgggaagg cagaggacaa ctacaagacc 1200
acgccggccg tgctggacag cgacggctcc tacttcctct acaacaagct ctcagtgccc 1260
acgagtgagt ggcagcgggg cgacgtcttc acctgctccg tgatgcacga ggccttgcac 1320
aaccactaca cgcagaagtc catctcccgc tctccgggta aa 1362

<210> 15
<211> 238
<212> PRT
<213> Oryctolagus cuniculus

<400> 15
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala
20 25 30
Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser
35 40 45
Ser Lys Asn Val Tyr Asn Asn Asn Trp Leu Ser Trp Phe Gln Gln Lys
50 55 60
Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Ala
65 70 75 80
Ser Gly Val Pro Ser Arg Phe Arg Gly Ser Gly Ser Gly Thr Gln Phe
85 90 95
Thr Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr
100 105 110
Cys Ala Gly Asp Tyr Ser Ser Ser Ser Asp Asn Gly Phe Gly Gly Gly
115 120 125
Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu
130 135 140
Phe Pro Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val
145 150 155 160
Cys Val Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val
165 170 175
Asp Gly Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln
180 185 190
Asn Ser Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr
195 200 205

Ser Thr Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln
210 215 220
Gly Thr Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys
225 230 235

<210> 16
<211> 717
<212> DNA
<213> Oryctolagus cuniculus

<400> 16
atggacacca gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60
agatgtgccg acgtcgtgat gacccagact ccagcctccg tgtctgcagc tgtgggaggc 120
acagtcacca tcaattgcca gtccagtaag aatgtttata ataacaactg gttatcctgg 180
tttcagcaga aaccagggca gcctcccaag ctcctgatct attatgcatc cactctggca 240
tctggggtcc catcgcggtt cagaggcagt ggatctggga cacagttcac tctcaccatt 300
agcgacgtgc agtgtgacga tgctgccact tactactgtg caggcgatta tagtagtagt 360
agtgataatg gtttcggcgg agggaccgag gtggtggtca aaggtgatcc agttgcacct 420
actgtcctcc tcttcccacc atctagcgat gaggtggcaa ctggaacagt caccatcgtg 480
tgtgtggcga ataaatactt tcccgatgtc accgtcacct gggaggtgga tggcaccacc 540
caaacaactg gcatcgagaa cagtaaaaca ccgcagaatt ctgcagattg tacctacaac 600
ctcagcagca ctctgacact gaccagcaca cagtacaaca gccacaaaga gtacacctgc 660
aaggtgaccc agggcacgac ctcagtcgtc cagagcttca gtaggaagaa ctgttaa 717

<210> 17
<211> 452
<212> PRT
<213> Oryctolagus cuniculus

<400> 17
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Ile Ser
35 40 45
Asp Tyr Asp Leu Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Lys
50 55 60
Tyr Ile Gly Phe Ile Ala Ile Asp Gly Asn Pro Tyr Tyr Ala Thr Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95

Lys Ile Thr Ala Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Gly Ala Gly Asp Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser
115 120 125

Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro Cys Cys
130 135 140

Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys Leu Val Lys Gly
145 150 155 160

Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Thr Leu Thr
165 170 175

Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser Ser Gly Leu Tyr
180 185 190

Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser Gln Pro Val Thr
195 200 205

Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro Pro Glu Leu Leu
225 230 235 240

Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile Asn Asn Glu Gln
275 280 285

Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln Phe Asn Ser Thr
290 295 300

Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp Leu Arg
305 310 315 320

Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu Pro Lys
340 345 350

Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg Ser Val
355 360 365

Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile Ser Val
370 375 380

Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr Thr Pro
385 390 395 400

Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys Leu Ser
405 410 415

Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile Ser Arg
435 440 445

Ser Pro Gly Lys
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<210> 18
<211> 1356
<212> DNA
<213> Oryctolagus cuniculus

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acagtctctg gattcaccat cagtgactac gacttgagct gggtccgcca ggctccaggg 180
gaggggctga aatacatcgg attcattgct attgatggta acccatacta cgcgacctgg 240
gcaaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatcaccgct 300
ccgacaaccg aagacacggc cacgtatttc tgtgccagag ggcaggggga cctctggggc 360
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gccccctgct gcggggacac accctctagc acggtgacct tgggctgcct ggtcaaaggc 480
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gacaagaccg ttgcgccctc gacatgcagc aagcccacgt gcccaccccc tgaactcctg 720
gggggaccgt ctgtcttcat cttcccccca aaacccaagg acaccctcat gatctcacgc 780
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ggcaaggagt tcaagtgcaa agtccacaac aaggcactcc cggcccccat cgagaaaacc 1020
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gaggagctga gcagcaggtc ggtcagcctg acctgcatga tcaacggctt ctacccttcc 1140
gacatctcgg tggagtggga gaagaacggg aaggcagagg acaactacaa gaccacgccg 1200
gccgtgctgg acagcgacgg ctcctacttc ctctacaaca agctctcagt gcccacgagt 1260
gagtggcagc ggggcgacgt cttcacctgc tccgtgatgc acgaggcctt gcacaaccac 1320
tacacgcaga agtccatctc ccgctctccg ggtaaa 1356

<210> 19
<211> 238
<212> PRT
<213> Oryctolagus cuniculus

<220>
<221> SITE

<222> (1)...(238)
<223> Xaa = any amino acid

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35 40 45
Gln Ser Val Tyr Asp Asn Asp Glu Leu Ser Trp Tyr Gln Gln Lys Pro
50 55 60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Lys Leu Ala Ser
65 70 75 80
Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Ala
85 90 95
Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110
Gln Ala Thr His Tyr Ser Ser Asp Trp Tyr Leu Thr Phe Gly Gly Gly
115 120 125
Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu
130 135 140
Phe Pro Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val
145 150 155 160
Cys Val Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val
165 170 175
Asp Gly Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln
180 185 190
Asn Ser Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr
195 200 205
Ser Thr Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln
210 215 220
Gly Thr Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys
225 230 235

<210> 20
<211> 717
<212> DNA
<213> Oryctolagus cuniculus

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cagcagaaac cagggcagcc tcccaagctc ctgatctatc tggcatccaa gttggcatct 240
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ggcgtgcagt gtgacgatgc tgccacttac tactgtcaag ccactcatta tagtagtgat 360
tggtatctta ctttcggcgg agggaccgag gtggtggtca aaggtgatcc agttgcacct 420
actgtcctcc tcttcccacc atctagcgat gaggtggcaa ctggaacagt caccatcgtg 480
tgtgtggcga ataaatactt tcccgatgtc accgtcacct gggaggtgga tggcaccacc 540
caaacaactg gcatcgagaa cagtaaaaca ccgcagaatt ctgcagattg tacctacaac 600
ctcagcagca ctctgacact gaccagcaca cagtacaaca gccacaaaga gtacacctgc 660
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<210> 21
<211> 454
<212> PRT
<213> Oryctolagus cuniculus

<400> 21
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Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Arg Ser
35 40 45
Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Val Gly Val Ile Ser Thr Ala Tyr Asn Ser His Tyr Ala Ser Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Asp Leu
85 90 95
Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Gly Gly Ser Trp Leu Asp Leu Trp Gly Gln Gly Thr Leu Val Thr
115 120 125
Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro
130 135 140
Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys Leu Val
145 150 155 160
Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Thr
165 170 175
Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser Ser Gly
180 185 190

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Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser Gln Pro
        195                 200                 205
Val Thr Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val Asp Lys
    210                 215                 220
Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro Pro Glu
225                 230                 235                 240
Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270
Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile Asn Asn
        275                 280                 285
Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln Phe Asn
    290                 295                 300
Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp
305                 310                 315                 320
Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro
                325                 330                 335
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu
            340                 345                 350
Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg
        355                 360                 365
Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380
Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr
385                 390                 395                 400
Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys
                405                 410                 415
Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys
            420                 425                 430
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile
        435                 440                 445
Ser Arg Ser Pro Gly Lys
    450

<210> 22
<211> 1362
<212> PRT
<213> Oryctolagus cuniculus

<400> 22
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20 25 30

Cys Gly Cys Thr Gly Thr Gly Cys Thr Cys Ala Ala Ala Gly Gly Thr

35 40 45

Gly Thr Cys Cys Ala Cys Thr Gly Thr Cys Ala Gly Thr Cys Gly Gly

50 55 60

Thr Gly Gly Ala Gly Gly Ala Gly Thr Cys Cys Gly Gly Gly Gly Gly

65 70 75 80

Thr Cys Gly Cys Cys Thr Gly Gly Thr Cys Ala Cys Gly Cys Cys Thr

85 90 95

Gly Gly Gly Ala Cys Ala Cys Cys Cys Cys Thr Gly Ala Cys Ala Cys

100 105 110

Thr Cys Ala Cys Cys Thr Gly Cys Ala Cys Ala Gly Cys Cys Thr Cys

115 120 125

Thr Gly Gly Ala Thr Thr Cys Thr Cys Cys Cys Gly Cys Ala Gly Cys

130 135 140

Ala Gly Cys Thr Ala Cys Gly Ala Cys Ala Thr Gly Ala Gly Cys Thr

145 150 155 160

Gly Gly Gly Thr Cys Cys Gly Cys Cys Ala Gly Gly Cys Thr Cys Cys

165 170 175

Ala Gly Gly Gly Ala Ala Gly Gly Gly Gly Cys Thr Gly Gly Ala Ala

180 185 190

Thr Gly Gly Gly Thr Cys Gly Gly Ala Gly Thr Cys Ala Thr Thr Ala

195 200 205

Gly Thr Ala Cys Thr Gly Cys Thr Thr Ala Thr Ala Ala Cys Thr Cys

210 215 220

Ala Cys Ala Cys Thr Ala Cys Gly Cys Gly Ala Gly Cys Thr Gly Gly

225 230 235 240

Gly Cys Ala Ala Ala Ala Gly Gly Cys Cys Gly Ala Thr Thr Cys Ala

245 250 255

Cys Cys Ala Thr Cys Thr Cys Cys Ala Gly Ala Ala Cys Cys Thr Cys

260 265 270

Gly Ala Cys Cys Ala Cys Gly Gly Thr Gly Gly Ala Thr Cys Thr Gly

275 280 285

Ala Ala Ala Ala Thr Gly Ala Cys Cys Ala Gly Thr Cys Thr Gly Ala

290 295 300

Cys Ala Ala Cys Cys Gly Ala Ala Gly Ala Cys Ala Cys Gly Gly Cys

305 310 315 320

Cys Ala Cys Cys Thr Ala Thr Thr Thr Cys Thr Gly Thr Gly Cys Cys

325 330 335

Ala Gly Ala Gly Gly Gly Gly Gly Thr Ala Gly Thr Thr Gly Gly Thr

340 345 350
Thr Gly Gly Ala Thr Cys Thr Cys Thr Gly Gly Gly Gly Cys Cys Ala
355 360 365
Gly Gly Gly Cys Ala Cys Cys Cys Thr Gly Gly Thr Cys Ala Cys Cys
370 375 380
Gly Thr Cys Thr Cys Cys Thr Cys Ala Gly Gly Gly Cys Ala Ala Cys
385 390 395 400
Cys Thr Ala Ala Gly Gly Cys Thr Cys Cys Ala Thr Cys Ala Gly Thr
405 410 415
Cys Thr Thr Cys Cys Cys Ala Cys Thr Gly Gly Cys Cys Cys Cys Cys
420 425 430
Thr Gly Cys Thr Gly Cys Gly Gly Gly Gly Ala Cys Ala Cys Ala Cys
435 440 445
Cys Cys Thr Cys Thr Ala Gly Cys Ala Cys Gly Gly Thr Gly Ala Cys
450 455 460
Cys Thr Thr Gly Gly Gly Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys
465 470 475 480
Ala Ala Ala Gly Gly Cys Thr Ala Cys Cys Thr Cys Cys Cys Gly Gly
485 490 495
Ala Gly Cys Cys Ala Gly Thr Gly Ala Cys Cys Gly Thr Gly Ala Cys
500 505 510
Cys Thr Gly Gly Ala Ala Cys Thr Cys Gly Gly Gly Cys Ala Cys Cys
515 520 525
Cys Thr Cys Ala Cys Cys Ala Ala Thr Gly Gly Gly Gly Thr Ala Cys
530 535 540
Gly Cys Ala Cys Cys Thr Thr Cys Cys Cys Gly Thr Cys Cys Gly Thr
545 550 555 560
Cys Cys Gly Gly Cys Ala Gly Thr Cys Cys Thr Cys Ala Gly Gly Cys
565 570 575
Cys Thr Cys Thr Ala Cys Thr Cys Gly Cys Thr Gly Ala Gly Cys Ala
580 585 590
Gly Cys Gly Thr Gly Gly Thr Gly Ala Gly Cys Gly Thr Gly Ala Cys
595 600 605
Cys Thr Cys Ala Ala Gly Cys Ala Gly Cys Cys Ala Gly Cys Cys Cys
610 615 620
Gly Thr Cys Ala Cys Cys Thr Gly Cys Ala Ala Cys Gly Thr Gly Gly
625 630 635 640
Cys Cys Cys Ala Cys Cys Cys Ala Gly Cys Cys Ala Cys Cys Ala Ala
645 650 655
Cys Ala Cys Cys Ala Ala Ala Gly Thr Gly Gly Ala Cys Ala Ala Gly
660 665 670
Ala Cys Cys Gly Thr Thr Gly Cys Gly Cys Cys Cys Thr Cys Gly Ala

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        675                 680                 685
Cys Ala Thr Gly Cys Ala Gly Cys Ala Ala Gly Cys Cys Cys Ala Cys
    690                 695                 700
Gly Thr Gly Cys Cys Cys Ala Cys Cys Cys Cys Cys Thr Gly Ala Ala
705                 710                 715                 720
Cys Thr Cys Cys Thr Gly Gly Gly Gly Gly Gly Ala Cys Cys Gly Thr
                725                 730                 735
Cys Thr Gly Thr Cys Thr Thr Cys Ala Thr Cys Thr Thr Cys Cys Cys
            740                 745                 750
Cys Cys Cys Ala Ala Ala Ala Cys Cys Cys Ala Ala Gly Gly Ala Cys
        755                 760                 765
Ala Cys Cys Cys Thr Cys Ala Thr Gly Ala Thr Cys Thr Cys Ala Cys
    770                 775                 780
Gly Cys Ala Cys Cys Cys Cys Cys Gly Ala Gly Gly Thr Cys Ala Cys
785                 790                 795                 800
Ala Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly Ala Cys
                805                 810                 815
Gly Thr Gly Ala Gly Cys Cys Ala Gly Gly Ala Thr Gly Ala Cys Cys
            820                 825                 830
Cys Cys Gly Ala Gly Gly Thr Gly Cys Ala Gly Thr Thr Cys Ala Cys
        835                 840                 845
Ala Thr Gly Gly Thr Ala Cys Ala Thr Ala Ala Ala Cys Ala Ala Cys
    850                 855                 860
Gly Ala Gly Cys Ala Gly Gly Thr Gly Cys Gly Cys Ala Cys Cys Gly
865                 870                 875                 880
Cys Cys Cys Gly Gly Cys Cys Gly Cys Cys Gly Cys Thr Ala Cys Gly
                885                 890                 895
Gly Gly Ala Gly Cys Ala Gly Cys Ala Gly Thr Thr Cys Ala Ala Cys
            900                 905                 910
Ala Gly Cys Ala Cys Gly Ala Thr Cys Cys Gly Cys Gly Thr Gly Gly
        915                 920                 925
Thr Cys Ala Gly Cys Ala Cys Cys Cys Thr Cys Cys Cys Cys Ala Thr
    930                 935                 940
Cys Gly Cys Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys Thr Gly Gly
945                 950                 955                 960
Cys Thr Gly Ala Gly Gly Gly Gly Cys Ala Ala Gly Gly Ala Gly Thr
                965                 970                 975
Thr Cys Ala Ala Gly Thr Gly Cys Ala Ala Ala Gly Thr Cys Cys Ala
            980                 985                 990
Cys Ala Ala Cys Ala Ala Gly Gly Cys Ala Cys Thr Cys Cys Cys Gly
        995                 1000                1005
Gly Cys Cys Cys Cys Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Ala
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1010 1015 1020

Cys Cys Ala Thr Cys Thr Cys Cys Ala Ala Ala Gly Cys Cys Ala Gly

1025 1030 1035 1040

Ala Gly Gly Gly Cys Ala Gly Cys Cys Cys Cys Thr Gly Gly Ala Gly

1045 1050 1055

Cys Cys Gly Ala Ala Gly Gly Thr Cys Thr Ala Cys Ala Cys Cys Ala

1060 1065 1070

Thr Gly Gly Gly Cys Cys Cys Thr Cys Cys Cys Cys Gly Gly Gly Ala

1075 1080 1085

Gly Gly Ala Gly Cys Thr Gly Ala Gly Cys Ala Gly Cys Ala Gly Gly

1090 1095 1100

Thr Cys Gly Gly Thr Cys Ala Gly Cys Cys Thr Gly Ala Cys Cys Thr

1105 1110 1115 1120

Gly Cys Ala Thr Gly Ala Thr Cys Ala Ala Cys Gly Gly Cys Thr Thr

1125 1130 1135

Cys Thr Ala Cys Cys Cys Thr Thr Cys Cys Gly Ala Cys Ala Thr Cys

1140 1145 1150

Thr Cys Gly Gly Thr Gly Gly Ala Gly Thr Gly Gly Gly Ala Gly Ala

1155 1160 1165

Ala Gly Ala Ala Cys Gly Gly Gly Ala Ala Gly Gly Cys Ala Gly Ala

1170 1175 1180

Gly Gly Ala Cys Ala Ala Cys Thr Ala Cys Ala Ala Gly Ala Cys Cys

1185 1190 1195 1200

Ala Cys Gly Cys Cys Gly Gly Cys Cys Gly Thr Gly Cys Thr Gly Gly

1205 1210 1215

Ala Cys Ala Gly Cys Gly Ala Cys Gly Gly Cys Thr Cys Cys Thr Ala

1220 1225 1230

Cys Thr Thr Cys Cys Thr Cys Thr Ala Cys Ala Ala Cys Ala Ala Gly

1235 1240 1245

Cys Thr Cys Thr Cys Ala Gly Thr Gly Cys Cys Cys Ala Cys Gly Ala

1250 1255 1260

Gly Thr Gly Ala Gly Thr Gly Gly Cys Ala Gly Cys Gly Gly Gly Gly

1265 1270 1275 1280

Cys Gly Ala Cys Gly Thr-Cys Thr Thr Cys Ala Cys Cys Thr Gly Cys

1285 1290 1295

Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Cys Gly Ala Gly Gly

1300 1305 1310

Cys Cys Thr Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala

1315 1320 1325

Cys Ala Cys Gly Cys Ala Gly Ala Ala Gly Thr Cys Cys Ala Thr Cys

1330 1335 1340

Thr Cys Cys Cys Gly Cys Thr Cys Thr Cys Cys Gly Gly Gly Thr Ala

1345 1350 1355 1360
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<210> 23
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 23
Ser Tyr Asp Met Thr
1 5

<210> 24
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 24
Ser Tyr Asp Met Ser
1 5

<210> 25
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<212> PRT
<213> Oryctolagus cuniculus

<400> 25
Asp Tyr Asp Leu Ser
1 5

<210> 26
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 26
Ser Tyr Asp Met Ser
1 5

<210> 27
<211> 8

<212> PRT
<213> Oryctolagus cuniculus

<400> 27
Tyr Ala Ser Gly Ser Thr Tyr Tyr
1 5

<210> 28
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<213> Oryctolagus cuniculus

<400> 28
Ser Ser Ser Gly Thr Thr Tyr Tyr
1 5

<210> 29
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<212> PRT
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<400> 29
Tyr Ala Ser Gly Ser Thr Tyr Tyr
1 5

<210> 30
<211> 8
<212> PRT
<213> Oryctolagus cuniculus

<400> 30
Ala Ile Asp Gly Asn Pro Tyr Tyr
1 5

<210> 31
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<400> 31
Ser Thr Ala Tyr Asn Ser His Tyr
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<210> 32
<211> 11
<212> PRT
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<400> 32
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<210> 33
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<400> 33
Glu Gly Ala Gly Val Ser Met Thr
1 5

<210> 34
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<400> 34
Glu Asp Ala Gly Phe Ser Asn Ala
1 5

<210> 35
<211> 4
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<400> 35
Gly Ala Gly Asp
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<210> 36
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<212> PRT
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<400> 36

Gly Gly Ser Trp Leu Asp
1 5

<210> 37
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<213> Oryctolagus cuniculus

<400> 37
Arg Cys Ala Tyr Asp
1 5

<210> 38
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<213> Oryctolagus cuniculus

<400> 38
Arg Cys Ala Asp Val Val
1 5

<210> 39
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<400> 39
Arg Cys Ala Leu Val
1 5

<210> 40
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<212> PRT
<213> Oryctolagus cuniculus

<400> 40
Gln Ser Ile Ser Thr Tyr
1 5

<210> 41
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<213> Oryctolagus cuniculus

<400> 41

Gln Ser Val Ser Ser Tyr
1 5

<210> 42
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<212> PRT
<213> Oryctolagus cuniculus

<400> 42

Glu Ser Ile Ser Asn Tyr
1 5

<210> 43
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<213> Oryctolagus cuniculus

<400> 43

Lys Asn Val Tyr Asn Asn Asn Trp
1 5

<210> 44
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<400> 44

Gln Gln Gly Tyr Thr His Ser Asn Val Asp Asn Val
1 5 10

<210> 45
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<400> 45

Gln Gln Gly Tyr Ser Ile Ser Asp Ile Asp Asn Ala
1 5 10

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<400> 46
Gln Cys Thr Ser Gly Gly Lys Phe Ile Ser Asp Gly Ala Ala
1 5 10

<210> 47
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<213> Oryctolagus cuniculus

<400> 47
Ala Gly Asp Tyr Ser Ser Ser Ser Asp Asn Gly
1 5 10

<210> 48
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<213> Oryctolagus cuniculus

<400> 48
Gln Ala Thr His Tyr Ser Ser Asp Trp Leu Thr Tyr
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<210> 49
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<220>
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<400> 49
auuua 5

<210> 50
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<220>
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<400> 50
auuuua 6

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<220>
<223> AU-rich sequence

<400> 51
auuuuua 7

<210> 52
<211> 157
<212> PRT
<213> Oryctolagus cuniculus

<400> 52
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20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45
Ser Tyr Asp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Ile Gly Ile Ile Tyr Ala Ser Gly Ser Thr Tyr Tyr Ala Ser Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95
Glu Val Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ser
100 105 110
Arg Glu His Ala Gly Tyr Ser Gly Asp Thr Gly His Leu Trp Gly Pro
115 120 125
Gly Thr Leu Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val
130 135 140
Phe Pro Leu Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser

145 150 155

<210> 53
<211> 154
<212> PRT
<213> Oryctolagus cuniculus

<400> 53
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20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35 40 45
Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Tyr Ile Gly Ile Ile Ser Ser Ser Gly Thr Thr Tyr Tyr Ala Asn Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95
Lys Val Thr Ser Pro Thr Ile Gly Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Glu Gly Ala Gly Val Ser Met Thr Leu Trp Gly Pro Gly Thr Leu
115 120 125
Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu
130 135 140
Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser
145 150

<210> 54
<211> 154
<212> PRT
<213> Oryctolagus cuniculus

<400> 54
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Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45
Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu

50 55 60
Trp Ile Gly Ile Ile Tyr Ala Ser Gly Ser Thr Tyr Tyr Ala Ser Trp
65 70 75 80
Ala Lys Gly Arg Val Ala Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95
Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Glu Asp Ala Gly Phe Ser Asn Ala Leu Trp Gly Pro Gly Thr Leu
115 120 125
Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu
130 135 140
Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser
145 150

<210> 55
<211> 147
<212> PRT
<213> Oryctolagus cuniculus

<400> 55
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1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30
Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45
Gln Ser Ile Ser Thr Tyr Leu Asp Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60
Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val
65 70 75 80
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
85 90 95
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110
Gly Tyr Thr His Ser Asn Val Asp Asn Val Phe Gly Gly Gly Thr Glu
115 120 125
Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro
130 135 140
Pro Ser Ser
145

<210> 56

<211> 147
<212> PRT
<213> Oryctolagus cuniculus

<400> 56
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20 25 30
Val Glu Val Ala Val Gly Gly Thr Val Ala Ile Lys Cys Gln Ala Ser
35 40 45
Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60
Pro Pro Lys Pro Leu Ile Tyr Glu Ala Ser Met Leu Ala Ala Gly Val
65 70 75 80
Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95
Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110
Gly Tyr Ser Ile Ser Asp Ile Asp Asn Ala Phe Gly Gly Gly Thr Glu
115 120 125
Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro
130 135 140
Pro Ser Ser
145

<210> 57
<211> 150
<212> PRT
<213> Oryctolagus cuniculus

<400> 57
Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala
20 25 30
Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala
35 40 45
Ser Glu Ser Ile Ser Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly
50 55 60
Gln Pro Pro Lys Leu Leu Ile Tyr Arg Thr Ser Thr Leu Ala Ser Gly
65 70 75 80

Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu
85 90 95
Thr Ile Ser Gly Val Gln Cys Asp Asp Val Ala Thr Tyr Tyr Cys Gln
100 105 110
Cys Thr Ser Gly Gly Lys Phe Ile Ser Asp Gly Ala Ala Phe Gly Gly
115 120 125
Gly Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu
130 135 140
Leu Phe Pro Pro Ser Ser
145 150

<210> 58
<211> 236
<212> PRT
<213> Oryctolagus cuniculus

<400> 58
Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30
Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45
Gln Ser Ile Ser Thr Tyr Leu Asp Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60
Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val
65 70 75 80
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
85 90 95
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110
Gly Tyr Thr His Ser Asn Val Asp Asn Val Phe Gly Gly Gly Thr Glu
115 120 125
Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro
130 135 140
Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val Cys Val
145 150 155 160
Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val Asp Gly
165 170 175
Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln Asn Ser
180 185 190
Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr Ser Thr

195 200 205
Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln Gly Thr
210 215 220
Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys
225 230 235

<210> 59
<211> 711
<212> DNA
<213> Oryctolagus cuniculus

<400> 59
atggacatga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60
agatgtgcct atgatatgac ccagactcca gcctctgtgg aggtagctgt gggaggcaca 120
gtcaccatca agtgccaggc cagtcagagc attagtacct acttagactg gtatcagcag 180
aaaccagggc agcctcccaa gctcctgatc tatgatgcat ccgatctggc atctggggtc 240
ccatcgcggt tcaaaggcag tggatctggg acacagttca ctctcaccat cagcgacctg 300
gagtgtgccg atgctgccac ttactactgt caacagggtt atacacatag taatgttgat 360
aatgttttcg gcggagggac cgaggtggtg gtcaaaggtg atccagttgc acctactgtc 420
ctcctcttcc caccatctag cgatgaggtg gcaactggaa cagtcaccat cgtgtgtgtg 480
gcgaataaat actttcccga tgtcaccgtc acctgggagg tggatggcac cacccaaaca 540
actggcatcg agaacagtaa aacaccgcag aattctgcag attgtaccta caacctcagc 600
agcactctga cactgaccag cacacagtac aacagccaca aagagtacac ctgcaaggtg 660
acccagggca cgacctcagt cgtccagagc ttcagtagga agaactgtta a 711

<210> 60
<211> 456
<212> PRT
<213> Oryctolagus cuniculus

<400> 60
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45
Ser Tyr Asp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Ile Gly Ile Ile Tyr Ala Ser Gly Thr Thr Tyr Tyr Ala Asn Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu

85 90 95
Lys Val Thr Ser Pro Thr Ile Gly Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Glu Gly Ala Gly Val Ser Met Thr Leu Trp Gly Pro Gly Thr Leu
115 120 125
Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu
130 135 140
Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys
145 150 155 160
Leu Val Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser
165 170 175
Gly Thr Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser
180 185 190
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser
195 200 205
Gln Pro Val Thr Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val
210 215 220
Asp Lys Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro
225 230 235 240
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro
245 250 255
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
260 265 270
Val Asp Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile
275 280 285
Asn Asn Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln
290 295 300
Phe Asn Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln
305 310 315 320
Asp Trp Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala
325 330 335
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro
340 345 350
Leu Glu Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser
355 360 365
Ser Arg Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser
370 375 380
Asp Ile Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr
385 390 395 400
Lys Thr Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr
405 410 415
Asn Lys Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe

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            420                 425                 430
Thr Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        435                 440                 445
Ser Ile Ser Arg Ser Pro Gly Lys
    450                 455
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<210> 61
<211> 1368
<212> DNA
<213> Oryctolagus cuniculus

<400> 61

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atggagacag gcctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag      60
tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc     120
acagtctctg gattctccct cagcagctac gacatgacct gggtccgcca ggctccaggg     180
aaggggctgg aatggatcgg aatcatttat gctagtggta ccacatacta cgcgaactgg     240
gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa agtcaccagt     300
ccgacaatcg gggacacggc cacctatttc tgtgccagag agggggctgg tgttagtatg     360
accttgtggg gcccaggcac cctggtcacc gtctcctcag ggcaacctaa ggctccatca     420
gtcttcccac tggcccccctg ctgcggggac acaccctcta gcacggtgac cttgggctgc     480
ctggtcaaag gctacctccc ggagccagtg accgtgacct ggaactcggg caccctcacc     540
aatggggtac gcaccttccc gtccgtccgg cagtcctcag gcctctactc gctgagcagc     600
gtggtgagcg tgacctcaag cagccagccc gtcacctgca acgtggccca cccagccacc     660
aacaccaaag tggacaagac cgttgcgccc tcgacatgca gcaagcccac gtgcccaccc     720
cctgaactcc tggggggacc gtctgtcttc atcttccccc caaaacccaa ggacaccctc     780
atgatctcac gcacccccga ggtcacatgc gtggtggtgg acgtgagcca ggatgacccc     840
gaggtgcagt tcacatggta cataaacaac gagcaggtgc gcaccgcccg gccgccgcta     900
cgggagcagc agttcaacag cacgatccgc gtggtcagca ccctccccat cgcgcaccag     960
gactggctga ggggcaagga gttcaagtgc aaagtccaca acaaggcact cccggccccc    1020
atcgagaaaa ccatctccaa agccagaggg cagcccctgg agccgaaggt ctacaccatg    1080
ggccctcccc gggaggagct gagcagcagg tcggtcagcc tgacctgcat gatcaacggc    1140
ttctaccctt ccgacatctc ggtggagtgg gagaagaacg ggaaggcaga ggacaactac    1200
aagaccacgc cggccgtgct ggacagcgac ggctcctact tcctctacaa caagctctca    1260
gtgcccacga gtgagtggca gcggggcgac gtcttcacct gctccgtgat gcacgaggcc    1320
ttgcacaacc actacacgca gaagtccatc tcccgctctc cgggtaaa                 1368
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<210> 62
<211> 236
<212> PRT
<213> Oryctolagus cuniculus

<400> 62

Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Val Ala Val Gly Gly Thr Val Ala Ile Lys Cys Gln Ala Ser
35 40 45

Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Pro Pro Lys Pro Leu Ile Tyr Glu Ala Ser Met Leu Ala Ala Gly Val
65 70 75 80

Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Gly Tyr Ser Ile Ser Asp Ile Asp Asn Ala Phe Gly Gly Gly Thr Glu
115 120 125

Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro
130 135 140

Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val Cys Val
145 150 155 160

Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val Asp Gly
165 170 175

Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln Asn Ser
180 185 190

Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr Ser Thr
195 200 205

Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln Gly Thr
210 215 220

Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys
225 230 235

<210> 63
<211> 711
<212> DNA
<213> Oryctolagus cuniculus

<400> 63
atggacatga gggcccccac tcaactgctg gggctcctgc tgctctggct cccaggtgcc 60
agatgtgcct atgatatgac ccagactcca gcctctgtgg aggtagctgt gggaggcaca 120
gtcgccatca agtgccaggc cagtcagagc gttagtagtt acttagcctg gtatcagcag 180
aaaccagggc agcctcccaa gcccctgatc tacgaagcat ccatgctggc ggctggggtc 240
tcatcgcggt tcaaaggcag tggatctggg acagacttca ctctcaccat cagcgacctg 300

gagtgtgacg atgctgccac ttactattgt caacagggtt attctatcag tgatattgat 360
aatgctttcg gcggagggac cgaggtggtg gtcaaaggtg atccagttgc acctactgtc 420
ctcctcttcc caccatctag cgatgaggtg gcaactggaa cagtcaccat cgtgtgtgtg 480
gcgaataaat actttcccga tgtcaccgtc acctgggagg tggatggcac cacccaaaca 540
actggcatcg agaacagtaa aacaccgcag aattctgcag attgtaccta caacctcagc 600
agcactctga cactgaccag cacacagtac aacagccaca aagagtacac ctgcaaggtg 660
acccagggca cgacctcagt cgtccagagc ttcagtagga agaactgtta a 711

<210> 64
<211> 459
<212> PRT
<213> Oryctolagus cuniculus

<400> 64
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Ser Pro
20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35 40 45
Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Tyr Ile Gly Ile Ile Ser Ser Ser Gly Ser Thr Tyr Tyr Ala Ser Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95
Glu Val Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ser
100 105 110
Arg Glu His Ala Gly Tyr Ser Gly Asp Thr Gly His Leu Trp Gly Pro
115 120 125
Gly Thr Leu Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val
130 135 140
Phe Pro Leu Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr
145 150 155 160
Leu Gly Cys Leu Val Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr
165 170 175
Trp Asn Ser Gly Thr Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val
180 185 190
Arg Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr
195 200 205
Ser Ser Ser Gln Pro Val Thr Cys Asn Val Ala His Pro Ala Thr Asn
210 215 220

Thr Lys Val Asp Lys Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr
225 230 235 240
Cys Pro Pro Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro
245 250 255
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270
Cys Val Val Val Asp Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr
275 280 285
Trp Tyr Ile Asn Asn Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg
290 295 300
Glu Gln Gln Phe Asn Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile
305 310 315 320
Ala His Gln Asp Trp Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His
325 330 335
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg
340 345 350
Gly Gln Pro Leu Glu Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu
355 360 365
Glu Leu Ser Ser Arg Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe
370 375 380
Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu
385 390 395 400
Asp Asn Tyr Lys Thr Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr
405 410 415
Phe Leu Tyr Asn Lys Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly
420 425 430
Asp Val Phe Thr Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445
Thr Gln Lys Ser Ile Ser Arg Ser Pro Gly Lys
450 455

<210> 65
<211> 1377
<212> DNA
<213> Oryctolagus cuniculus

<400> 65
atggagacag gcctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60
tcggtggagg agtccggggg tcgcctggtc tcgcctggga cacccctgac actcacctgc 120
acagcctctg gattctccct cagtagctac gacatgagct gggtccgcca ggctccaggg 180
aaggggctgg aatacatcgg aatcattagt agtagtggta gcacatacta cgcgagctgg 240
gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgga agtgaccagt 300

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ctgacaaccg aggacacggc cacctatttc tgtagtagag aacatgctgg ttatagtggt     360
gatacgggtc acttgtgggg cccaggcacc ctggtcaccg tctcctcggg gcaacctaag     420
gctccatcag tcttcccact ggcccctgc tgcggggaca caccctctag cacggtgacc      480
ttgggctgcc tggtcaaagg ctacctcccg gagccagtga ccgtgacctg gaactcgggc     540
accctcacca atggggtacg caccttcccg tccgtccggc agtcctcagg cctctactcg     600
ctgagcagcg tggtgagcgt gacctcaagc agccagcccg tcacctgcaa cgtggcccac     660
ccagccacca acaccaaagt ggacaagacc gttgcgccct cgacatgcag caagcccacg     720
tgcccacccc ctgaactcct ggggggaccg tctgtcttca tcttcccccc aaaacccaag     780
gacaccctca tgatctcacg cacccccgag gtcacatgcg tggtggtgga cgtgagccag     840
gatgaccccg aggtgcagtt cacatggtac ataaacaacg agcaggtgcg caccgcccgg     900
ccgccgctac gggagcagca gttcaacagc acgatccgcg tggtcagcac cctccccatc     960
gcgcaccagg actggctgag gggcaaggag ttcaagtgca aagtccacaa caaggcactc    1020
ccggccccca tcgagaaaac catctccaaa gccagagggc agcccctgga gccgaaggtc    1080
tacaccatgg gccctccccg ggaggagctg agcagcaggt cggtcagcct gacctgcatg    1140
atcaacggct tctacccttc cgacatctcg gtggagtggg agaagaacgg gaaggcagag    1200
gacaactaca agaccacgcc ggccgtgctg gacagcgacg gctcctactt cctctacaac    1260
aagctctcag tgcccacgag tgagtggcag cggggcgacg tcttcacctg ctccgtgatg    1320
cacgaggcct tgcacaacca ctacacgcag aagtccatct cccgctctcc gggtaaa       1377
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<210> 66
<211> 150
<212> PRT
<213> Oryctolagus cuniculus

<400> 66

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                   10                  15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Ile Ser
        35                  40                  45
Asp Tyr Asp Leu Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Lys
    50                  55                  60
Tyr Ile Gly Phe Ile Ala Ile Asp Gly Asn Pro Tyr Tyr Ala Thr Trp
65                  70                  75                  80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95
Lys Ile Thr Ala Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110
Arg Gly Ala Gly Asp Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser
        115                 120                 125
Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro Cys Cys
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130 135 140
Gly Asp Thr Pro Ser Ser
145 150

<210> 67
<211> 152
<212> PRT
<213> Oryctolagus cuniculus

<400> 67
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val His Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Arg Ser
35 40 45
Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Val Gly Val Ile Ser Thr Ala Tyr Asn Ser His Tyr Ala Ser Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Asp Leu
85 90 95
Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Gly Gly Ser Trp Leu Asp Leu Trp Gly Gln Gly Thr Leu Val Thr
115 120 125
Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro
130 135 140
Cys Cys Gly Asp Thr Pro Ser Ser
145 150

<210> 68
<211> 149
<212> PRT
<213> Oryctolagus cuniculus

<400> 68
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala
20 25 30
Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser

35 40 45
Ser Lys Asn Val Tyr Asn Asn Asn Trp Leu Ser Trp Phe Gln Gln Lys
50 55 60
Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Ala
65 70 75 80
Ser Gly Val Pro Ser Arg Phe Arg Gly Ser Gly Ser Gly Thr Gln Phe
85 90 95
Thr Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr
100 105 110
Cys Ala Gly Asp Tyr Ser Ser Ser Ser Asp Asn Gly Phe Gly Gly Gly
115 120 125
Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu
130 135 140
Phe Pro Pro Ser Ser
145

<210> 69
<211> 149
<212> PRT
<213> Oryctolagus cuniculus

<220>
<221> SITE
<222> (1)...(149)
<223> Xaa = any amino acid

<400> 69
Met Asp Xaa Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Leu Val Met Thr Gln Thr Pro Ala Ser
20 25 30
Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser
35 40 45
Gln Ser Val Tyr Asp Asn Asp Glu Leu Ser Trp Tyr Gln Gln Lys Pro
50 55 60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Lys Leu Ala Ser
65 70 75 80
Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Ala
85 90 95
Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110
Gln Ala Thr His Tyr Ser Ser Asp Trp Tyr Leu Thr Phe Gly Gly Gly

115 120 125
Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu
130 135 140
Phe Pro Pro Ser Ser
5145